Key words: intraventricular haemorrhage, intracerebral haemorrhage, extra-ventricular drain, tissue plasminogen activator, thrombolytic, intracranial pressure, cerebral perfusion pressure, randomised clinical trial, CLEAR III

Thrombolytic removal of intraventricular haemorrhage in treating severe stroke: Results of the CLEAR III trial, a randomised, controlled trial

Prof. Daniel F. Hanley, MD,[1] Karen Lane, CMA,[1] Nichol McBee, MPH,[1] Wendy Ziai, MD,[1] Prof. Stanley Tuhrim, MD,[2] Prof Kennedy R. Lees, MD,[3] Jesse Dawson, MD,[3] Dheeraj Gandhi, MD,[4] Natalie Ullman, MPH,[1] W. Andrew Mould, MPHc,[1] Steven W. Mayo, PD,[5] Prof A.. David Mendelow, FRCS, PhD,[6] Barbara Gregson, PhD,[6] Prof. Kenneth Butcher, MD,[7] Prof. Paul Vespa, MD,[8] David W. Wright, MD,[9] Prof. Carlos S. Kase, MD,[10] J. Ricardo Carhuapoma, MD,[1] Penelope M. Keyl, PhD,[1] Prof. Marie Diener-West, PhD,[11] John Muschelli, PhD, [11] Joshua F. Betz, MS,[11] Carol B. Thompson, MS,[11] Elizabeth A. Sugar, PhD,[11] Gayane Yenokyan, MD, PhD,[11] Scott Janis, PhD,[12] Sayona John, MD,[13] Sagi Harnof, MD,[14] George A. Lopez, MD, PhD,[15] Prof. E. Francois Aldrich, MD,[4] Mark R. Harrigan, MD,[16] Safdar Ansari, MD,[17] Prof. Jack Jallo, MD, PhD,[18] Prof. Jean-Louis Caron, MD,[19] David LeDoux, MD,[20] Opeolu Adeoye, MD,[21] Prof. Mario Zuccarello, MD,[22] Prof. Harold P. Adams Jr., MD,[23] Michael Rosenblum, PhD,[11] Richard E. Thompson, PhD,[11] Prof. Issam A. Awad, MD,[23] for the CLEAR III Investigators

1. Johns Hopkins University, School of Medicine, Brain Injury Outcomes Division, Baltimore, Maryland
2. Icahn School of Medicine at Mount Sinai, New York, New York
3. University of Glasgow, Glasgow, UK
4. University of Maryland, Baltimore, Maryland
5. Emissary International LLC, Austin, Texas
6. Newcastle University, Newcastle upon Tyne, UK
7. University of Alberta, Edmonton, Alberta, Canada
8. University of California, Los Angeles, Los Angeles, California
9. Emory University, Atlanta, Georgia
10. Boston University, Boston, Massachusetts
11. Johns Hopkins University Bloomberg School of Public Health, Department of Biostatistics, Baltimore, Maryland

12. National Institutes of Health, National institute of Neurological Disorders and Stroke, Bethesda, Maryland
13. Rush University, Chicago, Illinois
14. Chaim Sheba Medical Center, Ramat Gan, Israel
15. University of Texas, Houston, Houston, Texas
16. University of Alabama at Birmingham, Birmingham, Alabama
17. University of Utah, Salt Lake City, Utah
18. Thomas Jefferson University Hospital, Philadelphia, Pennsylvania
19. University of Texas, San Antonio, San Antonio, Texas
20. North Shore Long Island Jewish Medical Center, Manhasset, New York
21. University of Cincinnati, Cincinnati, Ohio
22. University of Iowa, Iowa City, Iowa
23. University of Chicago, Chicago, Illinois

Corresponding author:

Prof. Daniel F. Hanley, MD

Jeffrey & Harriet Legum Professor

Acute Care Neurology

Division of Brain Injury Outcomes

Johns Hopkins University

1550 Orleans Street, 3M50 South

Baltimore, MD 21231

Abstract

Introduction: Intraventricular haemorrhage (IVH) is a subtype of intracerebral haemorrhage (ICH), with 50% mortality and serious disability for survivors. CLEAR III, a randomised, double-blinded, placebo-controlled trial of subjects with a routinely-placed extraventricular drain (EVD), tested whether attempting to remove IVH with alteplase vs. saline irrigation improved functional outcome.

Methods: Patients in the intensive care unit with stable, non-traumatic ICH volume <30 mL, IVH obstructing the 3rd or 4th ventricles, and no underlying pathology were adaptively randomised (1:1) to receive up to 12 doses, 8 hours apart of 1mg of alteplase or 0.9% saline via the EVD. CT scans were obtained every 24 hours throughout dosing. The primary efficacy outcome was good functional outcome, defined as a modified Rankin Scale score of ≤3 at 180 days (mRS) per central adjudication by blinded evaluators.

Results: The trial completed with 180-day follow-up data available for analysis from 246/251 and 245/249 subjects in the alteplase and placebo groups, respectively. The primary efficacy outcome was similar in each arm (good outcome in alteplase group 48% vs. saline 45%; RR (95% CI)=1.06 (0.88, 128) p=0.554). A difference of 3.5% (RR (95% CI)=1.08 (0.90, 1.29), p=0.420) was found after adjusting for IVH size and thalamic ICH. At 180 days, the treatment arm had lower case fatality (18% vs. saline 29%, HR (95% CI)=0.60 (0.41, 0.86), p=0.006), but greater proportion with mRS 5 (17% vs. 9%; RR (95% CI)=1.99 (1.22, 3.26), p =0.005). Ventriculitis (7% alteplase vs. 12%; RR (95% CI)=0.55 (0.31, 0.97), p=0.048), and serious adverse events (49% alteplase vs. 63%; RR (95% CI)=0.77 (0.66, 0.91), p=0.002), were less frequent with alteplase treatment. Symptomatic bleeding (2%, both arms; RR (95% CI)=1.21 (0.37, 3.91), p=0.771) was similar.

Conclusions: In patients with IVH and a routine EVD, irrigation with alteplase did not substantially improve functional outcomes at the mRS 3 cutoff compared to irrigation with saline. Protocol-based use of alteplase with EVD appears safe. Future investigation is needed to determine if a greater frequency of complete IVH removal via alteplase produces gains in functional status.

(Funded by the National Institute of Neurological Disorders and Stroke; ClinicalTrials.gov NCT00784134.)

Word count with research in context is 4669

Introduction: In patients with spontaneous intracerebral haemorrhage (ICH), intraventricular haemorrhage (IVH) is associated with devastating consequences.[1-4] Mortality is reported to be greater than 50%, with fewer than 20% of survivors having good functional outcomes. Mortality and function appear to be altered if thrombolytic is employed.[5,6] Systematic review, Meta-analysis suggest removal of IVH improves survival and long-term functional outcome by relieving acute obstructive hydrocephalus and reducing neurotoxicity.[5-9] We hypothesised that small ICH with large IVH describes a subgroup of ICH patients whose severe prognosis is reversible.[1,6] Thus we organised the Phase III *Clot Lysis: Evaluating Accelerated Resolution of IVH (CLEAR III)* trial.

In EVD-treated IVH subjects, we tested the hypothesis that irrigating the ventricle with alteplase would be superior to normal saline (0.9%), measured by an improved modified Rankin Scale (mRS) score 0-3 (mRS ≤3, called “good outcome”), in which a score of 0 indicates no symptoms, a score of 5 indicates severe disability, and a score of 6 indicates death. This hypothesis was based on our preliminary data showing alteplase (Genentech, Inc., San Francisco, CA) can safely remove clot from the ventricle, if precautions are taken to avoid re-activating brain bleeding, in patients treated with an EVD.[10-13] Although EVD placement is not standardised in practice for all cases of IVH, it is used to manage hydrocephalus and intracranial pressure (ICP). We included such patients in the CLEAR III study.

Methods

Trial Design and Participants: CLEAR III was a multicentre, randomised (1:1), prospective phase III trial[11] done at 73 sites in the US, Canada, Brazil, Israel, UK, Germany, Hungary, and Spain, following local and country ethics approval, testing a strategy of ventricular clearance with alteplase via EVDs placed for ICP control in subjects with a clinical diagnosis of obstructive hydrocephalus. Placement of an EVD pre-trial was a routine clinical care decision. Subjects were age 18-80 with known symptom onset within 24 hours of the initial computed tomography (CT) scan confirming IVH and 3rd or 4th ventricle obstruction. Eligibility criteria included supratentorial ICH volume ≤30 mL, measured by the ABC/2 method,[12] and clot stability (no measured expansion >5 mL) on repeat CT scan at least 6 hours after EVD placement.[13] Additional eligibility criteria

included an historical mRS ≤1, no limitations to care, and no ongoing coagulopathy, suspicion of aneurysm, arteriovenous malformation, or other vascular anomaly.[13] (See supplemental appendix, section 2a. Methodological details of the treatment protocol: Inclusion and Exclusion criteria for additional details.) All data were captured electronically and pertinent source documentation uploaded by local site personnel using an internet-based electronic data capture (EDC) system (VISION, Prelude Dynamics, LLC, Austin, Tx). The EDC provided field-level and form-to-form range and value edit checks during data entry. Independent quality assurance monitors (Emissary International, LLC, Austin, Tx) utilized the uploaded source documentation to perform risk-based, remote monitoring of key data variables. Monitored data were then exported by the data management center where additional data edit checks were applied prior to form/subject finalization. Site personnel were notified of and responded to data discrepancies identified during these review processes using the EDC system query tool, with resulting data corrections captured by the electronic audit trail.

Randomization and Blinding: All subjects and trial personnel except for the local and central pharmacists and the unblinded statistician were masked to treatment assignments. After the local PI determined eligibility and written, informed consent was obtained, site personnel randomised patients within 72 hours of ictus using a web-based enrollment system (VISION, Prelude Dynamics, LLC, Austin, Tx), which generated a treatment allocation and emailed the treatment assignment code directly to the local, trained pharmacist. All other site and coordinating center personnel remained blinded to allocation. After 100 subjects were assigned by simple randomisation, a Pocock-Simon[14,15].covariate adaptive algorithm was implemented to balance study arms by baseline IVH size (≤20 mL; 20-50 mL; and >50 mL, measured on the diagnostic CT), ICH location (thalamus or other, determined by centralised CT reading). Imbalances in these factors were determined at each enrollment, and patients were randomised with a weighted coin (80/20) favoring assignment to the treatment arm, which improved balance in ICH location and ICH size. [6,13,14] To ensure treatment balance at the site, patients were adaptively randomised only after a given site had recruited two saline and two alteplase patients. All participants remained masked during data collection and interim analyses. Masking was evaluated by the external monitor.

Treatment: Subjects received up to 12 doses, 8 hours apart, of 1 mg of alteplase or 0.9% saline via the EVD. CT scans were obtained every 24 hours throughout dosing. All subjects were managed using the American Heart Association recommendations for the treatment of spontaneous ICH as the basis for a standard approach to airway, ventilation, ICP monitoring, sedation and pharmacologic treatment of mass effect.[16,17] Investigators were asked to remove as much clot as possible, until a stopping point was obtained: 3rd and 4th ventricles open; IVH mass effect relieved; 80% of clot was removed; or 12 doses were given.

Image analysis: To optimize accuracy and minimize investigator bias, clot volumes were analyzed by a core laboratory utilizing semi-automated segmentation and Hounsfield thresholds.[18] This was performed using OsiriX software (v.4.1, Pixmeo; Geneva, Switzerland) on DICOM images of each subject's stability and treatment scans. This approach has been validated for accuracy and inter-rater reliability.[19] Core lab values were utilized in all analyses. Core lab defined location as either thalamus or other (lobar, putamen, caudate).

Follow-up and Outcomes: Subjects were followed with an NIHSS assessment at Day 7, clinic visits on Days 30, 180, and 365, and phone contacts at Days 90 and 270. A site-identified, certified examiner assessed the mRS, extended Glasgow Outcome Scale (eGOS; 8 level disability scale from 8-upper good recovery to 1-death), Barthel Index (BI; 0 to 100 daily activities scale with 0 indicating no activities performed and 100 all activities performed), Stroke Impact Scale (SIS; self-reported scale of 16 activity domains from 1-most impaired to 5-not impaired), NIH Stroke Scale (NIHSS, clinic visits only; scores range from 0 to 42, with higher scores indicating a more severe neurologic deficit). CT was repeated at 30 and 365 days. The mRS assessment, the primary outcome, was video-recorded and sent to a core lab for blinded assessment by an independent panel of experts.[13] All other assessments were secondary. Full details of mRS, eGOS, and NIHSS are given in the supplemental appendix sections 2b and 2c.

Statistical Methods

Sample Size: The trial planning was informed by data from the previously completed Phase II CLEAR studies, which recorded 30-day outcomes.[6] Sample size planning assumed an average removal difference attributable

to alteplase of 12ml. The sample size of CLEAR III was planned to be 250 patients per group in order to provide at least 82% power to detect a risk difference of 13% in the proportion of good outcome from EVD+alteplase treatment compared to control, assuming a 22% proportion of good outcome among controls. The conjectured risk difference and good outcome rate under control were based on extrapolating from the previously completed Phase II CLEAR studies, which recorded baseline IVH clot volume and location (for ICH) and 30-day mRS outcomes.[6] To do this, models were first fit using the data from these studies, and then used for simulating hypothetical trials at sample size 500 as described in section 2g of the supplemental appendix.

We present data in three groups: the planned intention-to-treat (ITT) primary efficacy analyses of functional outcome; additional mRS efficacy analyses including other mRS analyses of various cut points, and secondary analyses of case fatality, clot removal, and ICU care; and safety. Adjusted analyses are indicated in Table S1. The primary and key secondary analyses were designated in 2008, at the start of the trial.

ITT Efficacy Analysis: The primary aim was to assess clinical efficacy of EVD+alteplase by estimating the difference in the proportion of centrally-adjudicated mRS scores, dichotomised as ≤3 vs. >3, at 180 days. We estimated the average benefit comparing treatment vs. control, using the ITT principle. Specifically, we estimated the difference between the probability of 180-day mRS ≤3, referred to as a good outcome, comparing alteplase vs. saline. In accordance with the literature on covariate-adaptive randomised designs, the estimate of the adjusted treatment effect was based upon a weighted average of the difference in proportions for each of the six strata defined by the possible baseline combinations for covariates used in randomization: IVH volume and location. Weights were set proportional to the number in each stratum (pooled across arms). The 95% confidence interval, estimated by the percentile method for the average treatment effect, was computed by the nonparametric bootstrap method, such that the covariate-adaptive design is adhered to in each resampled (i.e., bootstrap replicated) data set. Multivariable logistic regression models were used to estimate the conditional effect of treatment on good mRS outcome for baseline variables.

Secondary and Post-hoc Efficacy Analysis: Planned secondary efficacy analyses: 1) The Kaplan-Meier time-to-event analysis was used to estimate the survival functions and the log-rank test was used to compare

the survival by treatment. 2) A logistic model relating clot removed to mRS 0-3 proportion was used (Supplemental Table S2). These models were informed by univariate regression and well established clinical and epidemiologic considerations of the important prognostic factors of age, initial Glasgow Coma Scale (GCS) score (scores range from 3 to 15, with lower scores indicating reduced levels of consciousness), IVH size as a continuous variable, and the results of the planned intervention, clot removal. 3) Intensity of ICU management by treatment type was compared via Chi square or Fisher's exact test, as appropriate. Results of planned analyses of key demographic subgroups for heterogeneity of treatment effect: IVH and ICH size, location, GCS, age, gender, and race are presented.

Post hoc analyses were undertaken for two unexpected but clinically important findings: 1) when the number of subjects in mRS 5 category at 180 days was inspected for disproportion, a treatment comparison was made. 2) When inspection of protocol associated clot removal showed that alteplase achieved the hypothesised differential removal for subjects with IVH volume >20mL but not in the group with<20mL, subgroup by treatment group was undertaken. Interaction terms for treatment by baseline IVH stability volume at 20mL were considered. No correction for multiplicity was applied, as secondary analyses were considered hypothesis generating.

Safety Analysis: The safety aim of the trial was to achieve near total clot dissolution without procedure-related safety events endangering subjects beyond the risks associated with intensive medical treatment.[20] Analyses tested the null hypothesis that use of alteplase is safe for the treatment of IVH, relative to standard care of EVD alone under pre-specified thresholds for 30-day case fatality (40%), symptomatic rebleeding (25%), and bacterial brain infection (20%). We tested these three thresholds and all safety event rates as interim analyses after 100, 175, 250, and 350 subjects were enrolled and then for the full 500 over 180 days with Fisher's exact test. The overall occurrence rate of serious adverse events (SAEs) was tested between the two treatment groups.

Clot Removal Analysis: End of treatment (EOT) was defined as 24 hours after the last dose.[18] Additionally, area under the curve (AUC) of the IVH time course from stability to EOT was calculated using the trapezoidal

rule to quantify clot removal over time. AUC values were normalised by the time elapsed from stability to EOT to account for variability in treatment times. Logistic and Cox regression analyses were done to evaluate the relationship between IVH removal, represented by the normalised AUC of IVH clot on mRS ≤ 3, and 180-day case fatality, respectively, after adjustment for ICH clot location, age, ICH volume at stability and randomization GCS.

All analyses were conducted using two-sided tests with a Type I error rate of 0.05, performed using the statistical packages STATA 13.0 or higher (STATA Corp, College Station, TX) and R version 3.2 (R Foundation for Statistical Computing, Vienna, Austria). All data are presented as median [IQR: inter quartile range], unless otherwise specified.

Role of the Funding Source: The principal investigator (DFH) conceived, organized and executed this trial. He had full access to all study data and had final responsibility for the decision to submit for publication. The sponsor NIH/NINDS provided input regarding the study design during the grant review process and the NIH/NINDS-appointed DSMB provided the same during active recruitment. The NIH/NINDS-appointed DSMB and Genentech, Inc. approved the decision to submit the paper for publication.

Results

Subjects: Between September, 2009 and January, 2015, 500 patients were randomised, with the last subject completing follow-up in January, 2016 (Fig. 1). The trial completed with 180-day follow-up data available for analysis from 246/251 and 245/249 subjects in the alteplase and placebo groups, respectively. Admission demographics and clinical severity factors are shown in Table 1 and were similar between groups. Subjects arrived at hospital within 1.5 [0.8, 3.5] hours of ictus and underwent a CT by 2.3 [1.4, 4.9] hours. ICH clot location was thalamus 59%, 32% other; and 9% primary IVH (no identifiable ICH). The baseline IVH and ICH sizes were 21.8 [12.7, 36.9] mL and 7.9 [2.5, 15.0] mL, respectively. Baseline mean arterial pressure and ICP were similar by group. Subjects received first EVD at 7.5 [5.0, 12.0] hours and bleeding was determined stable by 43.5 [26.9, 57.9] hours post ictus.

Acute Protocol Period: Randomization occurred at 52.1 [39.1, 66.5] hours, with first treatment given 3.0 [1.7, 5.5] hours later. Five [3, 8] alteplase and 12 [9, 12] saline doses were given. EOT occurred at 2.5 [1.8, 3.7] and 4.7 [4.0, 5.1] days post randomization for alteplase and saline respectively. In the alteplase group, the 3rd and 4th ventricles opened more rapidly (p<0.0001). Twenty percent of all subjects achieved 80% removal of IVH, 10% saline and 30% alteplase. Overall, 27% of subjects received two EVDs (dual catheters), one in each lateral ventricle. During treatment, most subjects (78%) experienced at least one ICP reading ≥20mmHg. Cerebral perfusion pressure (CPP) <70 mmHg occurred in 62% of subjects despite continuous EVD drainage; the proportion of CPP compromise was 2% less in the alteplase arm (see Table 1). Permanent ventriculo-peritoneal shunts were placed in 18% of subjects.

Primary Efficacy Outcomes: Retention to day 180 was 98%. The primary ITT analysis comparing arms by mRS ≤3 outcome was 48% for alteplase and 45% for saline (RR (95% CI)=1.06 (0.88, 128), p = 0.554) (Fig. 2 and Table 2). The difference in good outcome (alteplase – saline) adjusted for IVH size and thalamic ICH was 3.5% (RR (95% CI)=1.08 (0.90, 1.29), p=0.420), not significantly different from zero. A single subject received alteplase after completion of 12 doses of saline (crossover). A subsequent sensitivity analysis was performed with this subject moved to the active treatment arm. The primary results did not change.

Secondary Outcomes and Safety: The mRS 6 (death) category showed a 50% decrease in the odds of being dead (mRS 6) for alteplase versus saline (Adjusted OR (95% CI) = 0.49 (0.37, 0.81), p = 0.001) (Table 3). No effect of hospital site was demonstrated for the primary mRS 0-3 outcome. (See Supplemental Table S1.) Estimated Kaplan-Meier survival probabilities were greater throughout 180 days of follow-up for the alteplase group (cumulative case fatality: 18% vs. 29%; p=0.006) (Fig. 3). Safety parameters favoured alteplase: bacterial ventriculitis (7% vs. 12%; RR (95% CI)=0.55 (0.31, 0.97), p=0.048) and SAEs (49% vs. 63%; RR (95% CI)=0.77 (0.66, 0.91), p=0.002). The frequency of symptomatic bleeding was similar between groups (2% in both arms; RR (95% CI)=1.21 (0.37, 3.91), p = 0.771). Table S1 in the supplemental appendix shows the primary, secondary and safety outcomes. Table 4 shows the safety profile by group and by the Medical Dictionary for Regulatory Activities (MedDRA) body system classifications.

A post-hoc analysis of the mRS 5 (i.e., bedbound) category shows a greater proportion in the alteplase group (17% vs. 9%; RR (95% CI)=1.99 (1.22, 3.26), p =0.005). Other post-hoc analyses demonstrated no difference in the proportion of subjects in a vegetative state, measured by the eGOS scale (3% in both groups; RR (95% CI)=1.33 (0.47, 3.78), p =0.787) nor for subjects surviving in long-term care facilities (alteplase 14% vs. saline 12%; RR (95% CI)=1.18 (0.74, 1.88), p =0.479) (see Fig. 2 and Table S2). Neither Barthel index nor EuroQol Visual Analog Scale (EQ-VAS; self-reported, quality of life scale with scores ranging from 0-worst to 100-best imaginable health state) was different between groups (see Table S1).

Clot Removal: Removal of clot varied widely, dependent on number and location of EVDs and number of alteplase doses. Thirty percent (30%) of the alteplase group and 10% of the saline group achieved the 80% removal endpoint. The planned secondary analysis relating mRS to the amount and timing of clot removal in all subjects demonstrated a significant relation between clot removal (per clot remaining (mL), as measured by normalised AUC) and both mRS ≤3 (AOR (95% CI)=0.96 (0.94, 0.97); p <0.0001) and case fatality (AHR (95% CI) of death per mL of time-weighted clot volume remaining = 1.03 (1.02, 1.04); p <0.0001), adjusted for age, thalamic ICH location, stability ICH volume, and randomised GCS (see Supplemental Table S3). The results of the subgroup analyses pre-specified in the protocol are shown in Supplemental Figure S1. No p values for interaction were significant.

Discussion

In the CLEAR III trial, irrigation of the ventricles with alteplase via a routine EVD did not improve functional outcomes in patients with IVH. Analyses of our secondary outcome measures, 180 day case fatality was significantly lower in the alteplase group, but the majority of these survivors ended up with severe disability (i.e., mRS4,5 or eGOS lower and upper significant disability). Clot removal analyses showed a correlation between amount of removal and improved mRS ≤3. Alteplase appears safe when compared to saline. These findings suggest possible value to the concept of removing greater amounts of IVH volume. On the face of the

current evidence, however, alteplase at the dose of 1 mg every 8 hours cannot be recommended as an intervention to improve functional outcome in patients with IVH.

There are limitations to this trial. This was the first Phase III IVH thrombolysis trial and evidence-based standards for subject selection and treatment endpoint did not exist. Current guidelines do not mandate the use, number, or location of EVD catheters, which are important factors influencing the amount of IVH removed. Routine practice produced good adherence to EVD safety, and opening of the midline ventricles occurred; but, poor adherence to removal of >80% IVH. This lack of adherence may have limited the stringency of the test of our hypothesis. Not all severity factors are known, so imbalances in severity could have existed. For example, nonspecific factors (e.g., type and extent of ICU care) could have been different between the treatment arms and influenced outcomes. For ICU care this does not seem likely, as subject severity, “withdrawal of care,” and ICU care were similar between groups. CLEAR III was a small sample of current clinical practice taken from the most aggressive end of the treatment spectrum: those subjects whose physicians utilised EVDs. The control intervention represents an aggressive level of care not always offered to every subject with IVH. The baseline mortality and good functional outcomes observed in the CLEAR III controls was greater than in our prior study[6] or in the expected levels from the general population (where low frequencies of EVD use are coupled with very high reliance on medical care as the sole supportive intervention for IVH).[2,3,6,7,9] Only convenience sample data exists for outcomes of medically managed subjects thus our knowledge about risk and benefit for the intervention in the general population is limited. Another possible limitation is that the CLEAR III sample might not represent a true general IVH population, rather a milder or more severe population. Evaluations of the general population of IVH, concurrently performed, have demographics and severity factors matching CLEAR III. They show full population estimates of mortality (40%-60%) and low good functional outcome (10%-30%) suggesting less intense therapies may not produce as many benefits.[2,5] Finally, the main outcome measure: mRS 0-3 vs. 4-6 proportion is only one measure of disability. Further research will be needed to clarify the divergent picture within the more severe disability segments of mRS and eGOS.[21] If survival comes at the cost of living with unacceptable impairment, this or any treatment could be seen as limited in value.

Potential to improve practice is evident with the findings that CPP/ICP are not always controlled by a single EVD routinely placed into the anatomically largest pool of cerebrospinal fluid or least bloody site. This is a starting point for investigating multiple catheters where clot is large, bilateral, trapping the ventricle, or creating a local mass effect. Placing a second catheter near or into the largest portion of the clot leads to greater and more rapid removal[22] and possibly greater clinical benefit. The precise clinical definitions for the at-risk population will need to be tested in a surgically-standardised trial setting.[23] The signal of benefit from greater clot removal and the low percentage of subjects achieving 80% removal raise the possibility that benefit of alteplase may be possible if greater clot removal could be achieved and, if it is achieved, more rapidly. As CLEAR III did not demonstrate improved rates of good functional recovery with alteplase rather than saline, future investigation will need improved surgical placement of catheters to achieve effective clot reduction more frequently and more rapidly. A possible solution is an adaptively-designed, efficacy-to-effectiveness trial[24] that demonstrates a better clot removal protocol can be integrated into routine stroke care and tests for influence on function, disability and case fatality.

Panel: Research in Context

Evidence before this study: A literature search was done from January 1, 1950 until November 1, 2015 on PubMed with the terms: IVH, IVH AND ICH, IVH AND TPA, IVH AND thrombolytic, IVH AND cross sectional, and IVH AND treatment. Search filters for "adult" and "human subjects" publications were applied. Meta-analysis of case series, one small multisite trial, and single-site convenience samples suggest mortality and perhaps functional impairment can be mitigated via enhanced clearance of the IVH through thrombolysis. Prior to and after the Clot Lysis: Evaluating Accelerated Resolution of IVH Phase III (CLEAR III) trial, when caring for patients with a small ICH and large IVH, clinicians have no class 1 evidence regarding the safety and effectiveness of IVH thrombolysis.

Added value of this study: CLEAR III is a randomised, double-blinded study designed to provide a test of the combination of extraventricular drainage (EVD) and low dose thrombolytic as a method of removing IVH and improving functional outcomes. This multisite study is the first to prospectively collect several objective

functional performance (modified Rankin Scale [mRS] and extended Glasgow Outcome Scale [eGOS]) as well as patient-based (Euro –QoL [EQ], Stroke Impact Scale [SIS]) measures of satisfaction. Medical care in the intensive care unit (ICU) was standardised and assessed rigorously. Data were prospectively defined and collected in a uniform manner and monitored thoroughly providing evidence of type, intensity and duration of ICU care required. Precise measurement of IVH size occurred in this trial possibly improving estimates of severity and treatment performance. The results of CLEAR III provide a robust estimate of the proportion of mRS 0-3 (approximately 45% to 48%) that occurs, if subjects are supported until the EVD is no longer needed. This led to an adjusted (IVH size and thalamic location) estimate of treatment effect of 3.5% (95% CI -4%, 12%). This effect size was not different between alteplase and saline treatment plans, though case fatality did differ. The absolute proportion of mRS 0-3 found in all CLEAR III subjects compares favourably to the untreated subjects in the literature. The study provides detailed evidence that a protocoled approach to remove IVH with alteplase is safe and that the 3rd and 4th ventricles open sooner if alteplase is utilized. A legitimate concern could be raised about greater infection rates due to frequent injections of alteplase or saline in the EVD, however a comparison of infection rate in CLEAR is in the same range as that reported in a meta-analysis of infections from published EVD series where injections were not performed. The data presented characterise substantial variations in current EVD-related neurosurgical practice. They demonstrate usefulness of the measures of initial severity (Glasgow Coma Scale [GCS], location, and ICH/IVH size) and the elements of treatment needed for precise characterization of prognosis in the aggressively treated IVH patient. The sub-group analysis suggests increased focus on larger IVH and earlier treatment times is appropriate.

Implications of all the available evidence: The trial was neutral on primary outcome of functional improvement. Therefore we do not think practice should change. Other post hoc results are consistent with the hypothesis that removal saves lives and possibly improves function. The issue of survival with disability is now well defined by our primary results and other measures of disability. The secondary results leave open a possible role of IVH volume reduction as a biomarker for treatment, with better outcomes more likely achieved with enhanced IVH clearance, particularly in subjects with larger initial IVH volume. The results are consistent with prior convenience reports and meta-analyses that good functional outcome can occur in up to 50% of treated subjects. The data provide a sound basis to critically redefine short-term neurosurgical and ICU management

around the task of volume removal. A trial testing these more objective goals is needed, if we are to be assured that aggressive removal of IVH is safe and can predictably produce increased independent function and decreased case fatality. Current information suggests as many as 25% of ICHs have large IVH. How many of these patients receive care and would be eligible for treatment is not known. An estimate of the full benefit of intervention will require a combined epidemiological and RCT intervention approach that randomises available subjects and collects information about usual care controls. A novel trial would provide a standardised surgical task, treat subjects more rapidly and require greater care team adherence to the removal of large amounts of the IVH, not just removal of enough blood clot to open the 3rd and 4th ventricles. Sharing the full results of CLEAR III is likely to stimulate further investigations of a worldwide problem that is serious, growing, and could be treatable.

Contributions. DFH and IAA organised the trial hypotheses, designed the trial, and provided guidance about the data analysis and interpretation/presentation of the data. DFH drafted most of the sections of the manuscript. KL, NMcB, WZ, ST, ADM, BG, KB, PV, DWW, PMK, MDW, SJo, SH, GL, EFA, MRH, SA, JJ, JLC, DL, OA, MZ, and HPA were involved in the design of the study and provided contributions to the writing and revising of the manuscript. KL, NMcB, and SWM organised and managed the trial including trial start-up, data collection, quality assurance, and trial close-out. KRL and JD provided the independent review and central adjudication of the modified Rankin Scale scores. DG, NU, and WAM provided the region of interest calculations for all volumetric measurement results. WZ, CSK, and JRC provided independent review and adjudication of all safety events. MR and RET generated the random allocation method. RET, JM, JFB, MR, CBT, EAS, and GY were involved in the statistical analysis, data interpretation, and contributed to the development and revisions to the manuscript. SJa provided critical review of the manuscript. The CLEAR III investigators contributed equally to the identification and, when eligible, randomization of trial participants.

Disclosures of Interest.

After funding of the trial by the United States National Institutes of Health, Genentech provided drug at no cost. This is not a regulatory study sponsored by Genentech. There has been no other scientific input from other companies or entities.

- H Adams reports grants from Johns Hopkins University, during the conduct of the study.
- S Ansari reports grants from National Institute of Neurological Disorders and Stroke, during the conduct of the study; personal fees from BARD MEDICAL, outside of the submitted work.
- I Awad reports grants from NIH/NINDS, during the conduct of the study.
- C Thompson reports grants from National Institute of Neurological Disorders and Stroke, during the conduct of the study.
- B Gregson reports grants from Johns Hopkins University (CLEAR III NIH grant), during the conduct of the study; grants from National Institute of Health Research (UK) HTA, outside the submitted work.
- D Hanley reports grants from NIH/NINDS, during the conduct of the study; grants and personal fees from EKOS Corp, grants and personal fees from Brainscope, personal fees from Rand Corp, personal fees from medico-Legal, outside the submitted work.
- M Harrigan reports grants from NIH, during the conduct of the study.
- K Lane reports grants from NINDS, during the conduct of the study.
- K Lees reports personal fees from Boehringer Ingelheim, outside the submitted work.
- S Mayo reports grants from NIH/NINDS, during the conduct of the study; personal fees from Johns Hopkins University, outside the submitted work.
- N McBee reports grants from National Institute of Neurological Disorders and Stroke, during the conduct of the study.
- AD Mendelow reports grants from NIH, during the conduct of the study; non-financial support from Director of Newcastle Neurosurgery Foundation Ltd, personal fees from Advisor to Stryker and Draeger, outside the submitted work.
- WA Mould reports grants from NINDS, during the conduct of the study.
- J Muschelli reports grants from T32AG000247 NIA Training Grant, during the conduct of the study.
- E Sugar reports grants from NIH/NINDS, during the conduct of the study.

- G Yenokyan reports grants from National Institute of Neurological Disorders and Stroke, during the conduct of the study; personal fees from The RAND Corporation, Health Advisory Services, outside the submitted work.
- W Ziai reports personal fees from HeadSense Medical, Inc., outside the submitted work.

The following authors have no conflicts of interest to disclose:
O Adeoye, EF Aldrich, J Betz, K Butcher, J Carhuapoma, JL Caron, J Dawson, M Diener-West, D Gandhi, S Harnof, J Jallo, S Janis, S John, C Kase, P Keyl, D LeDoux, G Lopez, M Rosenblum, R Thompson, S Tuhrim, N Ullman, D Wright, and M Zuccarello.

Acknowledgements. We wish to thank the CLEAR III patients and their families and the CLEAR III investigators and coordinators who provided and cared for them. We thank the Johns Hopkins University Brain Injury Outcomes (BIOS) Coordinating Center staff and site managers Bing Cao, Amanda Bistran-Hall, Tracey Hartmann and Noeleen Ostapkovich, the Reading Center readers, Timothy Morgan, Saman Nekoovaght-Tak, Hasan Ali, Vikram Madan, Alexandra Baker and Krissia Rivera Perla, and Coordinating Center Pharmacists, Janet Mighty and Esther Jeon; the University of Chicago Surgical Center managers, Agnieszka Stadnik, Jennifer Jaffe, and Michael Jesselson; Emissary International's Sarah Lenington, Nicki Karlen, and Carolyn Koenig for monitoring management; Prelude Dynamics for developing the data management and randomization systems; the Newcastle Neurosurgical Foundation and Mawdsleys-Brooks for supporting the trial in the European Union; the University of Glasgow outcomes assessors and translators and Robertson Centre for Biostatistics programmers; the Johns Hopkins Bloomberg School of Public Health Biostatistics Department data managers, Rachel Dlugash, Carol Thompson, Malathi Ram, Gwendolyn Clemens, Andre Hackman, and Jennifer Houser, Ryan Majkowski and Maningbe Kieta for their project management and technical editing. We thank the NIH-appointed DSMB Bob S. Carter, MD, PhD (Chairman), Kyra J. Becker, MD, James C. Torner, MS, PhD, and Alex B. Valadka, MD for their guidance and oversight of the safety of the trial participants. We also thank the FDA Orphan Products Development program for supporting a high-risk idea that became a program of investigation. CLEAR III was supported by the grant 5U01 NS062851-05,

awarded to Dr. Daniel Hanley from the National Institutes of Health (NIH), National Institute of Neurological Disorders and Stroke (NINDS).

Disclosures. Dr. Daniel F. Hanley was awarded significant research support of grants number R01NS046309, 5U01 NS062851-05, and 5U01 NS080824-02.

References

1. Hanley DF. Intraventricular hemorrhage severity factor and treatment target in spontaneous intracerebral hemorrhage. *Stroke* 2009; **40**(4): 1533-8.
2. Hansen BM, Morgan TC, Betz J, et al. Intraventricular Extension of Supratentorial Intracerebral Hemorrhage: The Modified Graeb Scale Improves Outcome Prediction in Lund Stroke Register. *Neuroepidemiology* 2015; **46**(1): 43-50.
3. Tuhrim S, Horowitz DR, Sacher M, Godbold JH. Volume of ventricular blood is an important determinant of outcome in supratentorial intracerebral hemorrhage. *Critical Care Medicine* 1999; **27**(3): 617-21.
4. Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. *New England Journal of Medicine* 2001; **344**(19): 1450-60.
5. Moradiya Y, Murthy SB, Newman-Toker DE, Hanley DF, Ziai WC. Intraventricular Thrombolysis in Intracerebral Hemorrhage Requiring Ventriculostomy A Decade-Long Real-World Experience. *Stroke* 2014; **45**(9): 2629-35.
6. Naff N, Williams MA, Keyl PM, et al. Low-Dose Recombinant Tissue-Type Plasminogen Activator Enhances Clot Resolution in Brain Hemorrhage The Intraventricular Hemorrhage Thrombolysis Trial. *Stroke* 2011; **42**(11): 3009-16.
7. Gaberel T, Magheru C, Parienti J-J, Huttner HB, Vivien D, Emery E. Intraventricular Fibrinolysis Versus External Ventricular Drainage Alone in Intraventricular Hemorrhage A Meta-Analysis. *Stroke* 2011; **42**(10): 2776-81.
8. Nieuwkamp DJ, de Gans K, Rinkel GJ, Algra A. Treatment and outcome of severe intraventricular extension in patients with subarachnoid or intracerebral hemorrhage: a systematic review of the literature. *Journal of Neurology* 2000; **247**(2): 117-21.
9. Staykov D, Bardutzky J, Huttner HB, Schwab S. Intraventricular fibrinolysis for intracerebral hemorrhage with severe ventricular involvement. *Neurocritical Care* 2011; **15**(1): 194-209.
10. Ziai WC, Muschelli J, Thompson CB, et al. Factors affecting clot lysis rates in patients with spontaneous intraventricular hemorrhage. *Stroke* 2012; **43**(5): 1234-9.
11. MIS+rtPA for ICH Evacuation (MISTIE).
12. Josephson CB, White PM, Krishan A, Al-Shahi Salman R. Computed tomography angiography or magnetic resonance angiography for detection of intracranial vascular malformations in patients with intracerebral haemorrhage. *The Cochrane Library* 2014.
13. Ziai WC, Tuhrim S, Lane K, et al. A multicenter, randomized, double-blinded, placebo-controlled phase III study of Clot Lysis Evaluation of Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III). *International Journal of Stroke* 2014; **9**(4): 536-42.
14. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975: 103-15.
15. Weir CJ, Lees KR. Comparison of stratification and adaptive methods for treatment allocation in an acute stroke clinical trial. *Statistics in Medicine* 2003; **22**(5): 705-26.
16. Morgenstern L, Hemphill 3rd J, Anderson C, et al. American Heart Association Stroke Council and Council on Cardiovascular Nursing. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2010; **41**(9): 2108-29.

17. Broderick J, Connolly S, Feldmann E, et al. American Stroke Association Stroke Council; American Heart Association/American Stroke Association High Blood Pressure Research Council; Quality of Care and Outcomes in Research Interdisciplinary Working Group. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American heart association/American stroke association stroke council, high blood pressure research council, and the quality of care and outcomes in research interdisciplinary working group. *Circulation* 2007; **116**(16): e391-413.
18. Mould WA, Carhuapoma JR, Muschelli J, et al. Minimally invasive surgery plus recombinant tissue-type plasminogen activator for intracerebral hemorrhage evacuation decreases perihematomal edema. *Stroke* 2013; **44**(3): 627-34.
19. Morgan TC, Dawson J, Spengler D, et al. The modified Graeb score an enhanced tool for intraventricular hemorrhage measurement and prediction of functional outcome. *Stroke* 2013; **44**(3): 635-41.
20. Mattle HP, Raabe A. CLEAR Intraventricular Hemorrhage More Than a Glimmer of Hope. *Stroke* 2011; **42**(11): 2999-3000.
21. TEASDALE GM, PETTIGREW LE, Wilson JL, MURRAY G, JENNETT B. Analyzing outcome of treatment of severe head injury: a review and update on advancing the use of the Glasgow Outcome Scale. *Journal of Neurotrauma* 1998; **15**(8): 587-97.
22. Hinson HE, Melnychuk E, Muschelli J, Hanley DF, Awad IA, Ziai WC. Drainage efficiency with dual versus single catheters in severe intraventricular hemorrhage. *Neurocritical Care* 2012; **16**(3): 399-405.
23. Vespa PM, Martin N, Zuccarello M, Awad I, Hanley DF. Surgical trials in intracerebral hemorrhage. *Stroke* 2013; **44**(6 suppl 1): S79-S82.
24. Selker HP, Oye KA, Eichler HG, et al. A proposal for integrated efficacy-to-effectiveness (E2E) clinical trials. *Clinical Pharmacology and Therapeutics* 2014; **95**(2): 147-53.

Table Notes and Figure Legends

Table Notes

Table 1. Demographic and Baseline Subject Characteristics by Group.

Table 2. Treatment Variables by Group. Additional Outcome Variable Data are Included as Table S4 in the Supplementary Materials.

Table 3. mRS Score Frequencies for the 30, 180, and 365 Day Time Points. The 180-Day Data Represent the Primary, Unadjusted Outcome. Corresponding eGOS Data for the Same Time Points Can Be Seen in Supplemental Table S3. In the alteplase group, one subject who was initially thought to be lost to follow-up at day 30 was located and evaluated at day 180.

Table 4. SAEs by treatment group. This listing shows fewer neurologic, respiratory, and sudden deaths (found in the MedDRA general disorders classification) in the alteplase group. This is consistent with the hypothesis that early removal of blood corrects a severe life threatening cerebral anatomic defect and possibly limits the structural brain injury as well as limits the effects of immobility on cardiorespiratory risks inherent with structural brain injury.

Figures Legends

Figure 1. CONSORT diagram. The CONSORT diagram summarizes the number of subjects that progressed through the enrollment, allocation, and follow-up periods of the trial. In the alteplase group, one subject who was initially thought to be lost to follow-up at day 30 was located and evaluated at day 180.

Figure 2. Outcome dichotomies of mRS (left panel; scores range from 0 [no disability] to 6 [death]) and eGOS (right panel; scores range from 8-upper good recovery to 1-death) scores at 30 and 180 days by treatment.

The left panel blue lines indicate the differences in proportion of 180-day mRS ≤ 3 (45% in saline vs. 48% in alteplase; p=0.477) and deceased subjects (30% in saline vs. 19% in alteplase; p=0.09).

Figure 3. Kaplan-Meier survival estimates with truncation at 193 days for late and missed 180-day visits (n=36), which corresponds to the longest "in-window" 180-day visit. Estimated survival probabilities were higher throughout 180 days of follow-up with alteplase compared to the saline group (p=0.006).

Table 1

	Alteplase (N=249)	**Saline (N=251)**
Demographic variables		
Age in Years: Median [IQR]	59 [51, 66]	59 [51, 67]
Gender: Female: no. (%)	105 (42)	117 (47)
Race White: no. (%) African American: no. (%) American Indian or Alaskan Native: no. (%) Other: no. (%)	 144 (58) 92 (37) 0 (0) 13 (5)	 161 (64) 78 (31) 1 (<1) 11 (4)
Ethnicity: Hispanic/Latino: no. (%)	28 (11)	32 (13)
Baseline variables		
Tobacco Use: no. (%)	73 (29)	59 (24)
Cocaine Use: no. (%)	12 (5)	18 (7)
Anticoagulated at Registration: no. (%)	20 (8)	29 (12)
Antihypertensive Med Compliant (self-report): no. (%)	168 (67)	202 (80)
Hyperlipidemia Med Compliant (self-report): no. (%)	240 (96)	245 (98)
On Antiplatelet at Registration: no. (%)	56 (22)	72 (29)
Randomization MAP: Median [IQR]	96 [86, 106]	94 [86, 104]
Randomization GCS† Total: Median [IQR]	10 [7, 13]	9 [7, 12]
Randomization NIHSS: Median [IQR]	(N=231) 19 [11, 32]	(N=232) 20 [11, 35]
Stability CT (last CT prior to enrollment) IVH Volume (mL): Median [IQR] ICH Volume (mL): Median [IQR]	 21.2 [12.6, 36.1] 8.2 [2.8, 15.2]	 22.4 [12.7, 39.1] 7.2 [2.3, 14.7]
Index Clot Location Thalamus: no. (%) Primary IVH: no. (%)	 149 (60) 18 (7)	 144 (57) 27 (11)
Ictus to Hospital Arrival (hrs.): Median [IQR]	1.5 [0.8, 3.4]	1.5 [0.8, 3.6]
Ictus to 1st CT (hrs.): Median [IQR]	2.3 [1.3, 4.6]	2.3 [1.4, 5.2]
Ictus to 1st EVD (hrs.): Median [IQR]	7.0 [4.5, 11.8]	7.9 [5.0, 12.0]
Ictus to Stability CT (hrs.): Median [IQR]	43.0 [25.4, 58.9]	44.0 [28.2, 57.0]
Ictus to Randomization (hrs): Median [IQR]	51.8 [36.4, 65.8]	52.2 [41.2, 66.8]

Table 2

	Alteplase (N=249)	Saline (N=251)	p-value
Treatment Variables			
Randomization to 1st Dose (hrs.): Median [IQR]	3.0 [1.7, 5.3]	3.1 [1.7, 5.7]	0.62
Total number of Doses: Median [IQR]	5 [3, 8]	12 [9, 12]	<0.001
Duration of Dosing (days): Median [IQR]	1 [1, 2]	4 [3, 4]	<0.001
Randomization to EOT (days): Median [IQR]	2.5 [1.8, 3.7]	4.7 [4.0, 5.1]	<0.001
EOT IVH Volume (mL): Median [IQR]	5.9 [1.9, 13.0]	11.5 [5.8, 23.1]	<0.001
Time to Open Ventricles (days): Median [IQR]	2 [2,3]	5 [3,7]	<0.001
ICP ≥20 mmHg: Mean proportion of events (mean of patient-specific proportions)	9.8	10.2	0.45
CPP <70 mmHg was lower with alteplase: no. (%)	644(7)	867(9)	<0.001
One or more ICP Therapy(ies): no. (%)	67 (27)	77 (31)	0.35
Dual EVD Placed: no. (%)	66 (27)	71 (28)	0.66
Day 0-180 Bacterial Ventriculitis: no. (%)	17 (7)	31 (12)	0.05
Symptomatic Bleeding ≤72 hr. post Last Dose: no. (%)	6 (2)	5 (2)	0.77
SAEs: no. (%)	121 (49)	158 (63)	0.002
Days in ICU: Median [IQR]	14 [11, 21]	15 [12, 22]	0.10
Withdrawal of Care: no. (%)	27 (11)	30 (12)	0.70
Ventilator Support: no. (%)	184 (74)	192 (76)	0.50
Pressor/Inotrope use: no. (%)	60 (24)	63 (25)	0.79
Ventriculoperitoneal Shunt: no. (%)	46 (18)	44 (18)	0.78

†Scores on the Glasgow Coma Scale (GCS) range from 15 (fully conscious) to 3 (deep coma)

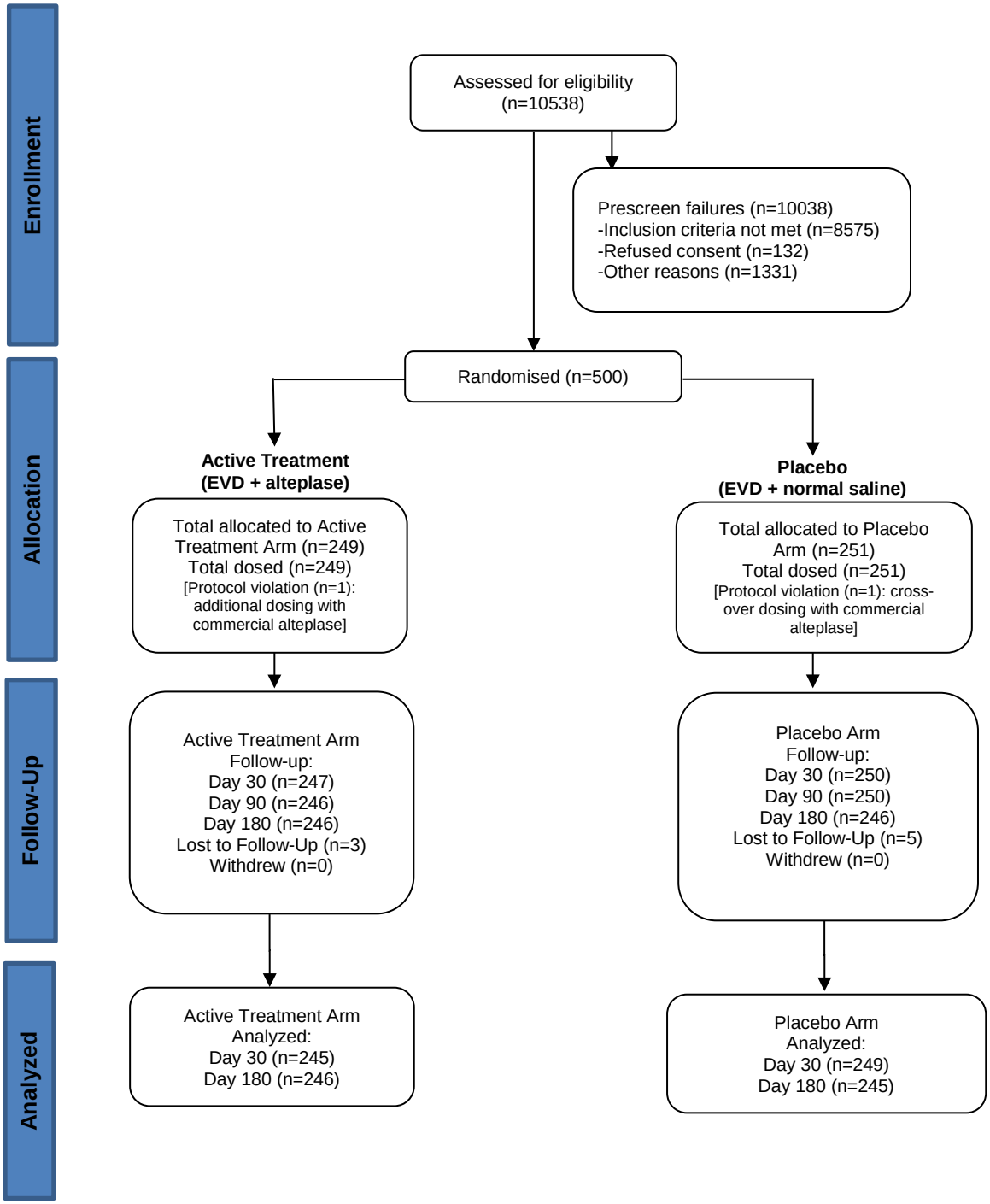
Table 3

	Visit and Treatment							
	30 days				180 days			
mRS	Saline (n=249)		Alteplase (n=245)		Saline (n=245)		Alteplase (n=246)	
0	4	1.61%	2	0.82%	11	4.49%	6	2.44%
1	2	0.80%	4	1.63%	13	5.31%	19	7.72%
2	7	2.81%	17	6.94%	31	12.65%	34	13.82%
3	28	11.24%	27	11.02%	55	22.45%	58	23.58%
4	46	18.47%	51	20.82%	41	16.73%	41	16.67%
5	126	50.60%	122	49.80%	21	8.57%	42	17.07%
6	36	14.46%	22	8.98%	73	29.80%	46	18.70%
Total	249	100.00%	245	100.00%	245	100.00%	246	100.00%

Table 4

Body System	Alteplase	Saline	
Blood and lymphatic disorders	0	1	
Cardiac disorders	7	14	
Gastrointestinal disorders	4	1	
General disorders and admin site conditions	22	34	
Hepatobiliary disorders	1	0	
Infections, non-neurologic	12	6	
Injury, poisoning and procedural complication	5	3	
Investigations (laboratory)	0	1	
Metabolism and nutrition disorders	0	1	
Musculoskeletal & connective tissue disorders	0	2	
Nervous system disorders	40	53	
Psychiatric disorders	1	2	
Renal and urinary disorders	2	2	
Respiratory, thoracic & mediastinal disorders	22	33	
Surgical and medical procedures	1	1	
Vascular disorders	4	4	
Total	**121**	**158**	
Percentage	**48.6%**	**62.9%**	p=0.0016

Figure 1


Enrollment
Allocation
Follow-Up
Analyzed
Assessed for eligibility (n=10538)
Prescreen failures (n=10038)
-Inclusion criteria not met (n=8575)
-Refused consent (n=132)
-Other reasons (n=1331)
Randomised (n=500)
Active Treatment (EVD + alteplase)
Placebo (EVD + normal saline)
Total allocated to Active Treatment Arm (n=249)
Total dosed (n=249)
[Protocol violation (n=1): additional dosing with commercial alteplase]
Total allocated to Placebo Arm (n=251)
Total dosed (n=251)
[Protocol violation (n=1): cross-over dosing with commercial alteplase]
Active Treatment Arm Follow-up:
Day 30 (n=247)
Day 90 (n=246)
Day 180 (n=246)
Lost to Follow-Up (n=3)
Withdrew (n=0)
Placebo Arm Follow-up:
Day 30 (n=250)
Day 90 (n=250)
Day 180 (n=246)
Lost to Follow-Up (n=5)
Withdrew (n=0)
Active Treatment Arm Analyzed:
Day 30 (n=245)
Day 180 (n=246)
Placebo Arm Analyzed:
Day 30 (n=249)
Day 180 (n=245)

Thrombolytic removal of intraventricular hemorrhage in treating severe stroke: Results of the CLEAR III trial, a randomised, controlled trial

Hanley DF, et al.
Supplemental Appendix

Table of Contents

1. List of sites, participating investigators and roles.

Site Name	PI	Lead Neurosurgeon (if not PI)	Study Coordinator	Number of Subjects Enrolled
Rush University	Sayona John	Lorenzo Munoz	Josephine Volgi	25
Chaim Sheba Medical Center	Sagi Harnof		Nina Levhar	24
University of Texas, Houston	George Lopez, Nicole Gonzales	P. Roc Chen	Chad Tremont	21
University of Maryland	E. Francois Aldrich		Charlene Aldrich	19
Johns Hopkins Hospital	Wendy Ziai	Judy Huang	Mirinda White	18
University of Alabama at Birmingham	Mark Harrigan		Lisa Nelson	17
Henry Ford Health System	Panayiotis Varelas	Donald Seyfried	Kathleen Wilson	16
University of Utah	Safdar Ansari	Richard Schmidt	Stephen Chatwin	14
NorthShore Long Island	David LeDoux	Salvatore Insinga	Tim White	13
Thomas Jefferson University Hospital	Jack Jallo		Kara Pigott	13
University of Texas, San Antonio	Jean-Louis Caron		Esther Nanez	13
University of Cincinnati	Opeolu Adeoye	Mario Zuccarello	Lynn Money	12
University of Iowa	Harold Adams	David Hasan	Heena Olalde	12
University of Heidelberg	Julian Bösel	Berk Orakcioglu	Perdita Beck	10
Case-Western Reserve University Hospital	Alan Hoffer		Valerie Cwiklinski	9
Maine Medical Center	David B. Seder	Jeff Florman	Barbara McCrum	9
University of Halle	Katja Wartenberg	Christian Strauss	Doreen Herale	9
University of Pittsburgh Medical Center	Lawrence Wechsler	Paul Gardner	Kara Armbruster	9
Allegheny General Hospital	Ashis H. Tayal	Khaled Aziz	Melissa Tian	8
Stanford University	Chitra Venkatasubramanian	Robert Dodd	Madelleine Garcia	8
UCLA	Paul Vespa		Courtney Real	8
University of Illinois at Chicago	Fernando Testai		Maureen Hillmann	8
University of Mainz	Thomas Kerz	Stefan Welschehold		8
Vall d'Hebron University Hospital, Barcelona	Fuat Arikan	Ramon Torne	Lourdes Exposito Mercedes Arrikas	8
Cedars-Sinai Medical Center	Asma Moheet		Felice Lin	7
Hadassah Hebrew University Hospital	Guy Rosenthal		Alex Furmanov	7
Penn State Hershey Medical Center	Kevin Cockroft		Deborah Hoffman	7
University of Buffalo	Jody Leonardo		Linda Bookhagen	7
University of Southampton Hospital	Diederik Bulters		Sophie Marlow Faith Vincent	7
Bellvitge Hospital, Barcelona	Alberto Torres Díaz		Meritxell Santos	6
Columbia University	Sachin Agarwal	E. Sander Connolly	Cristina Falo	6
Sourasky Medical Center Tel Aviv	Nevo Margalit	Erez Nossek	Carmit Ben Harosh	6
University of Alberta	Ken Butcher	Max Findlay	Leka Sivakumar	6
University of South Florida	David Decker	Siverio Agazzi	Denise Fife	6
Georgetown University	Mason Markowski		Courtney Hsieh	5
Hartford Hospital	Inam Kureshi		Sara Jasak	5
Providence Stroke Center	David Antezana	Lisa Yanese	Monica Rodriguez	5
Springfield Neurological and Spine Institute	H. Mark Crabtree		Jessica Ratcliff	5
University of Debrecen	Laszlo Csiba	Sandor Szabo	Katalin Szabó	5

Site Name	PI	Lead Neurosurgeon (if not PI)	Study Coordinator	Number of Subjects Enrolled
University of Leipzig	Dominik Michalski	Juergen Meixensberger	Daniela Urban	5
University of Pecs	Laszlo Szapary	Andras Buki	Peter Csecsei	5
Abington Memorial Hospital	Qaisar A.Shah	Steen J. Barrer	Karin Jonczak	4
Cooper University Hospital	Thomas Mirsen	Alan Turtz	Andrew March	4
Kansas University Medical Center	Paul Camarata		Jason Gorup	4
Mayo Clinic, Jacksonville	William Freeman	Ricardo Hanel	Alexa Richie	4
Medical University of South Carolina	Christos Lazaridis		Marc Lapointe	4
Ohio State University Medical Center	Michel Torbey	Ciaran Powers	Nirav Patel	4
SUNY Upstate Medical Center	Julius Gene Latorre	Eric Deshaies	Iulia Movileanu	4
University of Chicago	Agnieszka Ardelt	Issam Awad	Cedric McKoy	4
University of Tubingen	Sven Poli	Martin Schuhmann	Julia Zeller	4
Virginia Commonwealth University	R. Scott Graham		Kelly Mathern	4
Wake Forest University	Kristi Tucker	John Wilson	Sandra Norona	4
Yale University	David Greer	Murat Gunel	Kimberly Kunze	4
Montreal Neurological Institute at McGill University	David Sinclair		Steven Salomon	3
Mount Sinai	Stanley Tuhrim		Ricardo Renvill	3
Temple University Hospital	Michael Weaver		Carol Von Hofen / Kathleen Hatala	3
University of Erlangen	Hagen Huttner	Oliver Ganslandt	Anja Schmidt	3
University of Szeged	Pal Barzo	Zoltán Mencser	Eniko Fako	3
University of Texas, Southwestern, Dallas	Christiana Hall	Christopher Madden	Katrina Van De Bruinhorst	3
Vanderbilt	Michael Froehler	J Mocco	Emily Gilchrist	3
Hospital Sao Paulo Universidade Federal de Sao Paulo/UNIFESP	Gisele Sampaio Silva	Italo Caprano Suriano	Dirceu Regis, Raul Valiente	2
Hospital de Clinicas de Ribeirao Preto	Pedro Telles Cougo Pinto	Benedito Oscar Colli	Rodrigo Barbosa Cerantola	2
Hospital de la Santa Creu i Sant Pau, Barcelona	Joan Marti-Fabregas	Fernando Munoz	Rebeca Marin Bueno	2
Medical College of Wisconsin	Ann Helms	Wade Mueller	Alicia Constanquay	2
Saint Louis University	Salvador Cruz-Flores	Saleem Abdulrauf	Susan Eller	2
U Hosp, Inselspital, Bern	Michael Reinert		Ralph Schaer	2
University of Zurich	Andreas Luft	Betrand Actor	Benjamin Hertler	2
Mercy General Sacramento	Kavian Shahi		Susan Croopnick	1
New Jersey Neuroscience Institute at JFK	Martin Gizzi		Charles Porbeni	1
Newcastle General Hospital	A D Mendelow	Prokopios Panaretos, Francesco Vergani	Barbara Gregson	1
NorthShore Chicago	Issam Awad		Jen Jaffe	1
St. Luke's Brain and Stroke Institute, Kansas City	Darren Lovick		Bridget Brion	1
University of Southern California - Keck School of Medicine	Benjamin Emanuel	William Mack	Doris Arroyo	1
Albert Einstein Medical Center	George Newman	Mark Kotapka	Nwosu Chukwunweike John	0
Atlantic Neuroscience Institute	Igor Ugorec		Zenona Lesko	0
Boston University Medical Center	James Holsapple		Thai Q. Vu	0
Budapest - Honved Korhaz	Peter Bazso		Attila Josvai	0
Charite Universitatsmedizin in Berlin	Eric Juttler			0

Site Name	PI	Lead Neurosurgeon (if not PI)	Study Coordinator	Number of Subjects Enrolled
Duke University Medical Center	Michael Luke James		Ellen Bennett	0
Hospital Sao Jose, Joinville	Alexandre Luiz Longo	Andre Sanches Pitzschk	Juliana Antunes Safanelli	0
Hospital Universitario Clementino Fraga Filho	Jorge Marcondes de Souza		Marco Oliveira Py	0
Hospital de Clinicas de Porto Alegre	Sheila Cristina Ouriques Martins	Apio C. Martins Antunes	Natacha Fleck	0
Hospital de Pronto Socorro de Porto Alegre	Marcelo Kern	Rogerrio Symanski da Cunha	Susana Maria Endres	0
InterCoastal Medical Center	Mauricio Concha	Robert Knego	Jeanette Bryant	0
London University Health Sciences Centre	Mel Boulton		Robert Mayer	0
Loyola University Medical Center	Michael Schneck	Hazem M. Ahmed	Linda Chadwick	0
Massachusetts General Hospital	Christopher Ogilvy		Michael T Phillips	0
Mayo Clinic Arizona	Maria Aguilar	Richard Zimmerman	Patricia O'Donnell	0
Puerto Rico Medical Center	Fernando Santiago	Ricardo Brau	Ingrid Rodriguez	0
Rambam Medical Center	Menashe Zaaroor	Leon Levi	Efrat Velblum	0
Ruan Neurology Clinic and Research Center	Michael Jacoby	Robert Hirschl	Sheryl Inman	0
Salford Royal NHS Foundation Trust	Hiren Patel	John Kitchton	Victoria OLoughlin	0
Swedish Medical Center	David Newell		Jeannie Steed	0

2. Methods

2a. Methodological details of the treatment protocol

Eligibility Criteria:

Inclusion Criteria

1. Age 18-80.
2. Symptom onset less than 24 hrs prior to diagnostic CT scan.
3. Spontaneous ICH ≤ 30 cc and IVH obstructing 3rd and/or 4th ventricles.
4. ICH clot stability: ICH must be ≤ 30 cc on initial presentation and not exceed 35 cc on subsequent pre-randomization stability scans. A CT scan performed 6 hours or more after IVC placement must be stable (difference is ≤ 5 cc) compared to the most previous CT scan as determined by the (AxBxC)/2 method.
   Temporary Criterion: If the clot is not stable (i.e., difference is > 5 cc), a repeat CT scan must be performed at least 12 hours later and compared to the most previous CT scan. Investigator may continue to screen every 12 hours up to 72 hours for the initial bleeding to stabilize, as long as the subject is able to be randomized within 72 hours of time of diagnostic CT scan and the clot remains ≤ 35 cc. If the size stabilizes (i.e., enlargement ≤ 5 cc between 2 sequential CT scans) and remains ≤ 35 cc, the patient is eligible.
5. IVH clot stability: The width of the lateral ventricle most compromised by blood clot must not increase by > 2 mm, allowing for movement of blood under influence of gravity.
   Temporary Criterion: If the clot is not stable (i.e., difference is > 2 mm), a repeat CT scan must be performed at least 12 hours later and compared to the most previous CT scan. Investigator may continue to screen up to 72 hours for the initial bleeding to stabilize, as long as the subject is able to be randomized within 72 hours of time of diagnostic CT scan. If the size stabilizes (i.e., enlargement ≤ 2mm between 2 sequential CT scans), the patient is eligible.
6. Catheter tract bleeding must be less than or equal to 5 cc on CT scan for stability.
   Temporary criterion: If a catheter tract hemorrhage is present on the CT scan done 6 hours after IVC placement and is > 5 cc or > 5 mm, obtain a repeat CT scan 12 hours later. This includes any bleeding at the entry site or along the catheter tract that is 5 mm in diameter seen on any CT slice or is 5 mL on more than one CT slice. If the catheter tract hemorrhage further enlarges by > 5 cc or > 5 mm as compared to the most previous CT scan, the investigator may continue to screen by repeat CT scan every 12 hours for the bleeding to stabilize, as long as the subject is able to be randomized within 72 hours of time of diagnostic CT scan. If the size stabilizes (i.e., enlargement ≤ 5 cc or ≤ 5 mm between 2 sequential CT scans), the patient is eligible.
7. On stability CT scan, the 3rd and/or 4th ventricles are occluded with blood.
8. All patients randomized will have had EVD placed, ideally using no more than 2 complete passes (including "soft passes" using the original trajectory), on an emergent basis as defined by the "standard of care" neurosurgical/critical care decisions of the managing physicians. If more than 2 passes are required for placement, additional stabilization of IVC site will be determined with a CT performed at 24 hours after IVC placement.
   Temporary criterion: If no IVC is in place at the time the patient is initially screened, the decision to place an IVC may occur after the patient is initially screened but an IVC must be in-place and stable at the time of randomization.
9. Patients with primary IVH are eligible (i.e. with ICH=0).
10. SBP < 200 mmHg sustained for the 6 h before drug administration (closest to randomization).
    Temporary criterion: Blood pressure inclusion criteria not met when the patient is screened: Most vital signs are stabilized within the time window for enrollment.
11. No test article may be administered until at least 12 hours after symptom onset.
12. Able to randomize within 72 h of CT scan diagnosing IVH (provided the time of symptom onset to diagnostic CT does not exceed 24 h).
    Temporary criterion: The 72 hour limit may be extended with approval from the Coordinating Center to allow for clot stability (ICH, IVH, catheter tract), INR stability, or other valid reason.
13. Historical Rankin of 0 or 1.

Exclusion Criteria

1. Suspected (unless ruled out by angiogram or MRA/MRI) or untreated ruptured cerebral aneurysm, ruptured intracranial AVM, or tumor. Treatment of an existing aneurysm or AVM must have occurred at least 3 months before the current onset.

Temporary criterion: This is especially important in primary IVH, when no ICH source is found. CT angiogram, angiogram, MRA/MRI, or general diagnostic study (prior to confirming patient eligibility in the protocol) is standard of care to rule out underlying etiology. If the CT angiogram, angiogram or MRA/MRI is negative, the patient is eligible. The PI must document rationale if imaging is not done.

2. Presence of a choroid plexus vascular malformation or Moyamoya disease.
3. Clotting disorders. Subjects requiring long-term anti-coagulation are excluded.
   Temporary criterion: Reversing anticoagulation will be permitted where long-term anticoagulation is not required.
4. Use of Dabigatran, Apixaban, and/or Rivaroxaban (or a medication from the same medication class) prior to symptom onset.
5. Platelet count < 100,000, INR > 1.4.
   Temporary criterion: Low platelet counts etc. on admission can normalize within 24 hours as can an INR normalize to $\leq$ 1.4.
6. Pregnancy (positive serum or urine pregnancy test).
7. Infratentorial hemorrhage
8. Thalamic bleeds with apparent midbrain extension with third nerve palsy or dilated and non-reactive pupils. Other (supranuclear) gaze abnormalities are not an exclusion. Note: Patients with a posterior fossa ICH or cerebellar hematomas are ineligible.
9. SAH at clinical presentation (an angiogram (angiogram, CTA, MRA/MRI) must be obtained when the diagnostic CT scan shows SAH or any hematoma location or appearance not strongly associated with hypertension. If the angiogram or other imaging does not detect a bleeding source to account for the hemorrhage, the patient is eligible for the study.) Subsequent appearance of cortical SAH secondary to clot lysis is not a dosing endpoint.
   Temporary criterion: An angiogram must be obtained when the diagnostic CT scan demonstrates subarachnoid hemorrhage or any hematoma location suggestive of aneurysm or appearing not strongly associated with hypertension. If the angiogram/imaging does not demonstrate a bleeding source that accounts for the hemorrhage, the patient is eligible for the study.
10. ICH/IVH enlargement that cannot be stabilized in the treatment time window.
    Temporary criterion: ICH enlargement during the 6-hour stabilization period (6 hours after IVC placement): It is permitted to screen up to 72 hours after diagnostic scan. If the ICH clot size stabilizes (i.e., enlarges no more than 5 cc) and does not exceed 35 cc (an ICH clot size of 35 cc allows for stabilization of a 5cc expansion for those patients at the upper limit of the ICH clot size limit), the patient is eligible.
11. Ongoing internal bleeding, involving retroperitoneal sites, or the gastrointestinal, genitourinary, or respiratory tracts. (Patient with prior bleeding that is clinically stable for 12 h or more without any coagulopathy or bleeding disorder is eligible).
12. Multi-focal, superficial bleeding, observed at multiple vascular puncture and access sites (e.g., venous cutdowns, arterial punctures) or site of recent surgical intervention.
13. Prior enrollment in the study.
14. Any other condition that the investigator believes would pose a significant hazard to the subject if the investigational therapy were initiated. Subjects who are not expected to survive to the day 180 visit due to co-morbidities and/or are DNR/DNI status prior to randomization are excluded.
    Temporary criterion: Although these situations are often irreversible, under other conditions, change can occur over 24 hours.
15. Planned or simultaneous participation (between screening and Day-30) in another interventional medical investigation or clinical trial. Patients involved in observational, natural history, and/or epidemiological studies not involving an intervention are eligible.
16. No subject or legal representative to give written informed consent.

Stability Protocol: The risks of initial hematoma growth/instability were managed by use of a stability protocol combining normalization of coagulation parameters, blood pressure (BP) management, and repeat CT assessment of clot size measured using the ABC/2 method.[1] Six or more hours after the diagnostic CT, a stability CT was performed to ensure that the ICH clot was not expanding by >5 mL and that qualitative expansion in IVH had not occurred, providing image demonstration of a safe starting point for clot reduction therapy, defined as the absence of ongoing bleeding before randomization and initiation of test article. The CT could be repeated every six hours until the clot stabilized or just before the 72-hour eligibility window closed, whichever came first. In addition, a magnetic resonance image (MRI) or CT angiography (CTA) was encouraged as vascular pathology screening; an angiogram was encouraged where equivocal findings were noted on vascular pathology screening.[2] An INR $\leq$1.4, a platelet count > 100,000, and BP stability < 200 mm Hg were required prior to randomization.[3,4]

EVD management: The Surgical Center located at the University of Chicago actively reviewed all catheter placements and monitored clot removal assessments, catheter discontinuation protocols, and evaluated the safety and efficacy of the surgical procedure.[1] The Surgical Center recommended pull-back and/or replacement of catheters that were sub-optimally placed within the

ventricular system as well as placement of a second, concurrent catheter ipsilateral or contralateral to the most affected side for optimal test article delivery. Recommendations were not mandatory.

Test article administration protocol: Eligible subjects were adaptively randomized to receive intraventricular injections of either normal saline or alteplase. Local pharmacists were notified to prepare the assigned "test article" such that the clinicians remained blind to assignment. Intraventricular alteplase administrations of 1.0 mg in 1 mL were given every 8 hours, up to 12 doses, or until an endpoint was reached. All doses were followed by a 3 mL flush of preservative-free normal saline. After each assigned dose, the system was closed for one hour to allow drug-clot interaction, and then opened to allow for gravitational drainage. Trial-defined clinical endpoints included, opening of 3rd and 4th ventricles, mitigation of IVH-related mass effect, 80% reduction of clot volume measured on the stability CT, reaching a maximum of 12 doses or occurrence of a clinically significant bleeding event, defined as a clot enlargement accompanied by sustained drop of more than two points on the Glasgow Coma Scale (GCS) motor score with CT-demonstrated ICH enlargement. CT scans were subsequently obtained every 24 hours until dosing was complete to evaluate safety and drainage. Test article administration was performed under standard conditions to maintain sterile environment and cranial compartment euvolemia. Procedural training was mandatory. Selection of the dosing endpoint was determined on a subject-by-subject basis at each site.

Image analysis: To optimize accuracy and minimize investigator bias, clot volumes were analyzed by a core laboratory utilizing semi-automated segmentation and Hounsfield thresholds.[5] This was performed using OsiriX software (v.4.1, Pixmeo; Geneva, Switzerland) on DICOM images of each subject's stability and treatment scans. This approach has been validated for accuracy and inter-rater reliability.[6] Core lab values were utilized in all analyses. Core lab defined location as either thalamus or other (lobar, putamen, caudate).

Prohibited medications: The administration via any brain catheter of any thrombolytic agent (other than the study agent administered per protocol) was prohibited. Clogged catheters were flushed with normal saline. Antithrombotic and antiplatelet agents were prohibited prior to the day 30 follow-up visit. Enoxaparin at therapeutic doses ≥1,0 mg/kg subcutaneously every 12 hours was prohibited during the 12-month study period following randomization.

2b. Central adjudication of Rankin scale assessments (CARS)

CARS Infrastructure

The Central Adjudication of Rankin Scale assessments (CARS) system is a secure web based portal designed specifically for the upload and central adjudication of video recorded mRS endpoints in the CLEAR-III trial (https://www.glasgowctu.org/CLEAR3). The CARS portal was developed by staff of the Institute of Cardiovascular and Medical Sciences and technical support of the Robertson Centre for Biostatistics, both within the University of Glasgow. It provides fully validated backend study databases for collection of all Rankin scores and review decisions taken from endpoint committee members, where applicable.

The CARS systems are fully documented and incorporate a complete audit trail from upload to score. CARS is fully compliant with relevant GCP guidelines and was developed and validated in accordance with Computerised Systems for Clinical Research guidelines and 21 CRF Part 11 – Electronic Records and Electronic Signatures. Dates and times are recorded at both local and central database levels and are compliant with ISO 8601: 1988 (E) (Data elements and interchange formats – Information interchange – Representation of dates and times). The web pages are only accessible using secure socket layer (SSL) communication, which utilises a validation certificate created for a particular server within a specific domain. This enables authentication from the server to the user's browser and encrypts all traffic between their local computer and the authenticated host server. The web server is secured by VeriSign, the BT Trust Services Global Server Certificate program and is firewall-protected.

Training in Modified Rankin Scale Assessment: All CLEAR-III assessors (local and central) underwent training and certification in mRS assessment using an online training resource. Study staff were also provided with bespoke instruction for use of the CARS system in the trial, including guidance on mRS scoring and on conducting interviews for central review.

CARS Staff: The CARS system was overseen by a team at the University of Glasgow comprising an outcomes manager who oversaw the day to day running of the system, trained and experienced adjudicators, and a team of translators for relevant non-English languages.

Communication between CARS System and Trial Management Systems: The CARS portal was integrated with the CLEAR-III EDC managed by VISION during initial trial set up, such that investigators were able to upload assessments via the main trial management system in a secure manner. This simultaneously automated transfer of information (such as patient identification number, visit date, visit site and assessment language) to the CARS system. The same connection allowed the CARS system to return status

reports including 'successful upload' to the trial management system and ultimately to return the completed mRS score. Automated status updates were relayed to both the trial management system and the CARS team both on attempt and on completion of upload, to allow monitoring of video uploads and quick identification of any problem. All communications maintained blinding of the CLEAR-III coordinating center staff.

Addressing Technical difficulties: A technical support team based at the Robertson Centre of Biostatistics within the University of Glasgow was responsible for the maintenance of the CARS portal and responding to any issues that arose. Team members were available via telephone or email.

Performing and Uploading Modified Rankin Scale Assessments

Recording of the Modified Rankin Scale Assessment: A portable digital video camera with an in-built microphone was used to record the mRS interview. Video cameras were supplied through the CLEAR-III management team. Examples of models used are the FLIP Mino (CISCO systems, San Jose US) and the PIXPRO SPZ1 (Eastman Kodak Company, Rochester US). The assessor was directed to sit opposite the participant and beside (or holding) the camera, out of view. The camera was to be positioned a suitable distance from the participant so that the recording captured the participant's face and trunk. The videos were recorded in standard definition at 60fps ensuring a reasonable file size for upload. The CARS system handled a diverse range of commonly used file types such as .mp4, .wmv, .avi, .mov, .mpg, .mts and .m4v.

Upload of the Modified Rankin Scale Assessment: Upload was performed via the trial management system (VISION EDC), requiring trial staff only to have a single log in. The USB connections were used to connect the camera to a computer and to transfer files for upload. Users monitored progress of the upload via a status bar and received an automated notification upon successful upload.

Central Adjudication of Modified Rankin Scale Assessments

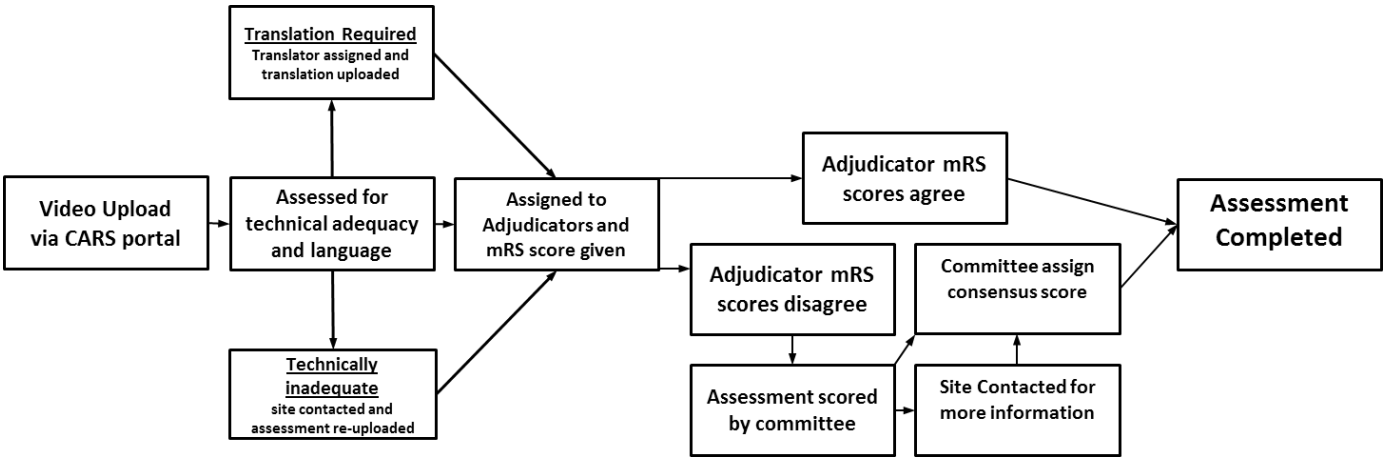
Initial Review for Technical Adequacy, Anonymity and Masking of Treatment Allocation: In the CLEAR-III trial an outcomes manager received an automated email upon successful upload of an assessment. The system would then block further upload of assessments for this participant. Upon receipt of successful upload notification, the outcomes manager reviewed the assessment for quality and maintenance of blinding. If the assessment was clearly inadequate, either in terms of technical factors (such as no audio, no patient visible, incorrect patient study identity or visit number) or was lacking in sufficient information to begin the scoring process, it was labelled with a status of 'technically inadequate.' This would prompt an automated message to the local investigator that further information or a replacement assessment was required. The CARS system would update the EDC and then allow further uploads to be submitted. Minor editing of assessments could be performed by the outcomes manager at this stage to preserve anonymity, masking of treatment allocation or to conceal details of the local score; such editing was tracked for audit purposes.

Translation of Non-English Language Clips: Non-English language assessments were sent for translation to a bilingual native speaker of that language, with experience in the use of the mRS. Translations were performed using a digital recording device and the ensuing audio file was uploaded directly to the CARS system, where the audio file was then merged (overdubbed) with the original video of the mRS assessment. Both the native language and translated assessment were available for review by the assigned adjudicators. Upon successful upload of a translation the outcomes manager again assessed the translations to ensure blinding and protection of patient confidentiality.

Review and Scoring of Assessments

Assessments were assigned to CARS reviewers, who would be contacted via an automated email containing a direct link to the assigned assessment in the CARS system. Reviewers each had unique login details to permit tracking of workload and quality. They could access the video clips via either desktop or portable devices, to allow timely review and scoring. Reviewers recorded their chosen score within the CARS portal while the relevant video recording was on screen, and were also asked to record comments to justify their choice of score, that would be helpful in the event of subsequent committee discussion.

In the CLEAR-III trial, the scoring algorithm accepted as final any score that agreed between the local and first central rater. However, if there was a discrepancy between the local and first CARS score, then the assessment proceeded to committee review, for which 3 further independent reviews of this assessment were performed. Once 4 scores had been independently assigned, the committee of these raters discussed the assessment and reached a consensus on final score. This consensus score was entered to the CARS portal by the committee chairman and the score was automatically returned to the VISION EDC. Tracking of the stages is possible.



Quality Control and Ongoing Training

We monitored inter-rater agreement for mRS scores, allowing us to optimize assessment guidance or to identify any rater who may benefit from additional training. We provided feedback to investigators at all sites and arranged refresher training in mRS assessment during the CLEAR-III trial via webinar sessions, including example video assessments.

CARS staff

Adjudicators:

Jen Alexander (Queen Elizabeth University Hospital Glasgow, UK), Jesse Dawson (University of Glasgow, UK), Peter Higgins (University of Glasgow, UK), Kennedy Lees (University of Glasgow, UK), Kate McArthur (University of Glasgow, UK), Terry Quinn (University of Glasgow, UK), Matthew Walters (University of Glasgow, UK), Alastair Wilson (University of Glasgow, UK)

Translators:

Sukainah Al Alshaikh (University of Glasgow, UK), Samantha Alvarez-Madrazo (University of Glasgow, UK), Péter Bukovics (University of Pecs, Hungary), Laila Day (University of Glasgow, UK), Catarina Fonseca (Universidade de Lisboa, Portugal), Benedikt Frank (University Hospital Essen, Germany), Nora Gonzalez (University of Glasgow, UK), Karim Hajjar (University Hospital Essen, Germany), Kerrick Hesse (University of Glasgow, UK), Nicki Karlen (Emissary LLC, Israel), Kitti Kovacs (University of Debrecen, Hungary), Ananada Mirchindani (University of Glasgow, UK), Guillaume Turc (Sainte-Anne Hospital Paris, France)

ACKNOWLEDGEMENTS

We thank all the outcomes assessors and translators who work across our various trials. The initial CARS studies were funded by a grant from the Chief Scientist Office Scotland (CZB/4/595).

2c. Training, including eGOS and NIHSS

Training modules were prepared for key personnel at the enrolling sites. Key personnel were defined as the principal investigator, coordinator, pharmacist and others designated to perform data collection, drug preparation, and drug administration.

Initial Training ensured that all site personnel were properly trained concerning FDA regulations, ICH guidelines, and trial policies and procedures. During the investigator start up meeting, the first training module included design and methods of the trial, the importance of integrity in acute and follow-up data collection, the need for data security, study organization, performance and compliance, and actual treatment procedures, and coordinators were required to work through sample VISION/Prelude EDC screens. The training modules were incorporated into the MOP. The CC worked with the site investigators to continuously identify and correct problems of compliance, data collection, outcomes assessment and data processing.

The following is the list of mandatory investigator/coordinator training modules:

Enrolling Site Training Events – New Personnel	Method	Site Initiation	Annual Recertification	Refresher
Design and methods of the trial Importance of integrity in data collection Need for data security Study organization Performance and compliance Treatment procedures Current Study Results	Power point presentation	✓		✓
Human Subjects HIPAA Ethics Conflicts of Interest	On-line training	✓		
Electronic Data Entry	On-line training	✓		
Sample Data Set	Hands on training	✓		
Web Site Access	On-line training	✓		
Modified Rankin Scale Certification	Video training and test	✓	✓	
NIHSS Certification ⇐	Video training and test	✓	✓	
eGOS, SIS, EQ, QOL, PBSI ⇐	Power point presentation	✓		
CT Stability Training	On-line training and certification	✓		✓
Drug Administration Certification	Video training and test	✓		
IVC Placement Certification	Power point presentation	✓		
Graeb Scoring Tutorial	Power-point presentation	✓		
Ventricular Opening Endpoints	Power-point presentation	✓		
Pharmacy Procedures	Power-point presentation	✓		
Recruitment and Consent	Power-point presentation	✓		
AE and SAE Reporting	Power-point presentation	✓		
Protocol Deviations	Power-point presentation	✓		
Study Progress and Procedural Changes	Power-point presentation	✓		
Protocol Test	Web-based Certification test	✓	✓	

Extended GOS (eGOS): Site personnel were trained on eGOS administration technique using a MS PowerPoint module developed by the CC. The eGOS was obtained by local, trained personnel as part of the follow-up procedures at days 30, 180, and 365. Proxy interview was utilized if the subject scored <18 on the Mini-Mental Status Examination. The eGOS was first recorded onto a paper bedside worksheet as source documentation and then entered into the VISION EDC system. These date were monitored by the QA Monitor for transcription errors and consistency among all other outcomes assessments.

NIHSS: Site personnel were instructed to utilize existing online NIHSS certification websites to obtain certification and then upload documentation of successful course completion to the VISION EDC electronic master file. Certification was obtained prior to the site initiation meeting with recertification required annually. NIHSS was captured if done by the clinical care team as close to the time of presentation as possible, and then done by a certified examiner at randomization, day 7, and again at follow-up days 30, 180, and 365. The NIHSS was the only outcomes assessment done at day 7. The interview was first recorded onto a paper bedside worksheet as source documentation and then entered into the VISION EDC system. These date were monitored by the QA Monitor for transcription errors and consistency among all other outcomes assessments.

2d. Severity Index Analysis

As an initial step in developing our severity index for predicting mRS (0-3), categories for well established “explanatory” variables: age, GCS at randomization, and stability ICH were created according to the distribution of the data for each variable. Two or more categories were combined if equally predictive of mRS (0-3), based on univariate logistic regression models. IVH and ICH location were set to their pre-specified values (i.e., < 20 mL, >= 20 – 50 mL, and > 50 mL, and thalamic and non-thalamic, respectively). The final categories considered were: Age (<=50 yrs, 50- <60 yrs, 60 – <65 yrs, 65 - <70 yrs, and >=70 yrs), GCS (<= 9, 10-12, and 13-15), ICH (<= 8 mL, >8 – 15 mL, > 15 mL), IVH (< 20 mL, >=20 – 50 mL, > 50 mL), and ICH location (thalamic, non-thalamic). Next, a multivariable logistic regression was created that regressed the binary outcome of mRS <=3 vs. mRS >3 on these 5 predictors. (Gender was considered in this model, but was determined to be non-significant, and therefore dropped).

Based on the coefficients of this model, the severity was created that weighed each category as follows: Severity Index = 1.0 *(1 if age >=50 and <60, 0 otherwise) + 1.3*(1 if age >=60 and <65, 0 otherwise) + 1.85*(1 if age >=65 and <70, 0 otherwise) + 2.0*(1 if age >=70, 0 otherwise) + 1.7*(1 if GCS <=9, 0 otherwise) + 1.0*(1 if GCS =10-12, 0 otherwise) + 0.8*(1 if thalamic, 0 otherwise) + 0.8*(1 if IVH >=20 and <=50, 0 otherwise) + 2.4*(1 if IVH >50, 0 otherwise) + 0.85*(1 if ICH >8 and <=15, 0 otherwise) + 2.0*(1 if ICH >15, 0 otherwise). This score gives a maximum possible value of 9.0; however the highest score seen in the data set was 8.85. A

score of 0 indicates the lowest severity (e.g., a patient with an age <=50 years, GCS >=13, IVH < 20 mL, ICH <=8 mL and non-thalamic ICH).

Regression of the odds of mRS (0-3) gives a decrease of approximately 63% in the odds of having a 180-day mRS <=3 for each one unit increase in the severity score, a result that is highly statistically significant (OR [95% CI] = 0.37 [0.31, 0.44], p < 0.001). Treatment assignment was not statistically significant once we controlled for severity by this index, a result that is consistent with that reported in Table S2 (Adj OR [95% CI] = 0.92 [0.59, 1.44], p = 0.716). In addition, there was no evidence of a treatment by severity interaction effect (p=0.973).

However, clot removal as measured by normalized AUC (as a percent of stability IVH), was significant once we controlled for severity (Adj OR [95% CI] = 0.998 [0.997, 1.000], p = 0.037). Again there was no evidence of an AUC by severity interaction effect (p=0.773).

A similar process was followed to create an index score to predict 180-day mortality. Categories of variables were slightly different than for the mRS (0-3) index, and thalamic location was not found to be predictive of mortality as compared to other ICH locations. The mortality score was created as follows: Mortality Index = 0.5 *(1 if age >=50 and <60, 0 otherwise) + 0.6*(1 if age >=60 and <65, 0 otherwise) + 1.0*(1 if age >=65 and <70, 0 otherwise) + 1.4*(1 if age >=70, 0 otherwise) + 0.8*(1 if GCS <=7, 0 otherwise) + 1.0*(1 if IVH >= 20 and < =50, 0 otherwise) + 1.7*(1 if IVH >50, 0 otherwise) + 0.9*(1 if ICH >15, 0 otherwise). This score gives a maximum possible value of 4.8, with the highest value seen in the data set of 4.8.

Regression of the odds of death at 180 days indicates just over a two-and-half fold increase in the odds of death for each one unit increase in the mortality score, a result that is highly statistically significant (OR [95% CI] = 2.74 [2.15, 3.49], p < 0.001). Treatment assignment was highly statistically significant once we controlled for the mortality index, a result that is consistent with our reported survival analyses (Adj OR [95% CI] = 2.01 [1.26, 3.20], p = 0.003, severity adjusted odds of death at 180 days for saline vs. alteplase). This effect was consistent across all levels of the mortality severity index.

2e. Analysis of Interaction between Age and Mortality

As shown in Figure S3 and Table S10, analyses of the interaction between age and mortality lend weight to our conclusion that alteplase reduces 180-day mortality compared to the saline-treated patients.

In our assessment of this possible interaction on mortality, we considered 1) the risk ratio (RR) of death across 5 strata of age (<50 yr, 50 - <60 yr, 60 - <65 yr, 65- <70 yr, and >70 yr), and 2) created a Cox model that incorporated an age (continuous variable) by treatment interaction.

We found that the RR varied from 0.42 – 0.80 across all five age strata, giving a Mantel-Haenszel combined RR = 0.64. We then tested the null hypothesis for homogeneity across age strata (chi2 [deg =4] = 1.41, p= 0.842), the non-significant finding is concordant with the presence of consistent relative risk across all age strata (e.g. no heterogeneity of treatment effect across age strata). Similarly, the age by treatment interaction term in the Cox model with both the main effects of age and treatment is not statistically significant (HR interaction = 1.01, p = 0.665). This suggests the effect of alteplase on mortality is not modified by age.

Therefore, based on these analyses, we concluded that the difference in mortality between treatment arms is consistent across every age strata, and there is no statistical evidence indicating an effect modification of age on the association between treatment and mortality.

2f. Summary of Protocol Amendments

v1.1 (8 Oct 2008) to v2.0 (15 Jun 2009)

- Vital signs monitoring/data collection frequency changed from q1hr to q4hr. Vital signs monitoring/data collection schedule changed from days 1 through ICU discharge to days 1-7 with daily assessment of ICP management beginning on day 8 and continuing through IVC removal. ICP management data will be collected retrospectively at hospital discharge and will be used to monitor compliance with EVD management/weaning protocol.
- Removed the GOS scale as an outcome scale. The GOS will now be computed from the extended GOS.
- Added the EQ-5D to the day 90 and 270 telephone follow-up visits.

- The Mini-Mental State Exam will now be administered to everyone, not just to subjects with GCS<15 as previously written.
- Exclusion criteria:
    - Added Moyamoya disease.
    - Lowered the acceptable INR from 1.7 to 1.3 for eligibility and for dosing. Also deleted PT as a determination of eligibility. Eligibility is now based on INR ≤1.3 and aPTT within normal limits.
- Deleted daily laboratory assessments of PT, fibrinogen, plasminogen, d-dimer. Now only collecting daily serum WBC, Hct, platelet count, INR, aPTT as well as daily CSF labs. Plasminogen and fibrinogen will be assessed once prior to first dose.
- Deleted IVC tip culture upon removal.
- Specified that all quality monitoring of subject data will be done remotely. The VISION/Prelude EDC system will be used to query the data. Source documentation may remain identified.

V2.0 (15 Jun 2009) to v3.0 (22 Mar 2011)

- Incorporated adaptive randomization.
- Added the Personal Health Utility Assessment Interview to the 180 day follow-up visit.
- Inclusion criteria:
    - Changed the enrollment window from first dose within 72 hours of diagnostic CT to randomization within 72 hours of diagnostic CT.
    - Raised the acceptable INR from 1.3 to 1.4.
- Permit use of heparin during the acute treatment period.
- Increased stability period from 12 to 24 hours during dosing.

V3.0 (22 Mar 2011) to v4.1 (17 Apr 2013)

- Added exclusion of patients taking Dabigatran.
- Allow the use of enoxaparin during dosing along with other low molecular weight heparins that are already considered Permitted Interventions.

V4.1 (17 Apr 2013) to v4.2 (1 Jull 2013)

- Added further exclusion from randomization of patients taking Apixaban, Rivaroxaban and similar medications in addition to Dabigatran.
- Added prohibition of Apixaban and Rivaroxaban in addition to Dabigatran through day 30.

2g. Monte Carlo simulations for sample size calculation

Power and sample size derivations were based on the 180-day outcomes, to yield minimum statistical power calculations. That is, the given sample size would have at least the reported power to observe a treatment difference at 180 days. Inclusion of additional data and information through the longitudinal analyses would serve to enhance model efficiency and thus increase power.

2g.1. Statistical Power - Primary Endpoint 1 (Modified Rankin Scale ≤3 at 180 days). Statistical power for primary endpoint 1 was derived from Monte Carlo simulation studies based on the empirical relationships observed in the previous Safety, CLEAR A and CLEAR B studies. mRS outcomes were simulated from sequential conditional distributions based on the previously observed data in the Safety, CLEAR part A, and CLEAR part B (24 patients) studies as follows:

$$F(\text{mRS, site, rt\_PA, IVH volume, ICH volume, ICH Clot Location})$$
$$= F(\text{mRS} \mid \text{site, rt\_PA, ivh\_10cc, ich\_10cc, location})$$
$$* F(\text{rt\_PA} \mid \text{ivh\_10cc, ich\_10cc, location})$$
$$* F(\text{ivh\_10cc} \mid \text{ich\_10cc, location})$$
$$* F(\text{ich\_10cc} \mid \text{location})$$
$$* F(\text{location})$$

Simulation data for power calculations was thus generated in five steps:

Step 1: Simulate clot locations. Clot locations in the 88 patients from the Safety, CLEAR part A and part B studies were distributed as: Thalamus, n=41 (47%); Caudate\Putamen, n= 16 (18%), Other location, n=10 (11%), No Measurable Clot, n=21 (24%). We used this information to guide clot locations in a simulated sample of size N=500 by drawing from a multinomial distribution with related probabilities. For example, in simulation dataset 1, we drew clot locations of: Thalamus, n=246 (49%); Caudate\Putamen, n= 134 (27%), Other location, n=57 (11%), No Measurable Clot, n=63 (13%).

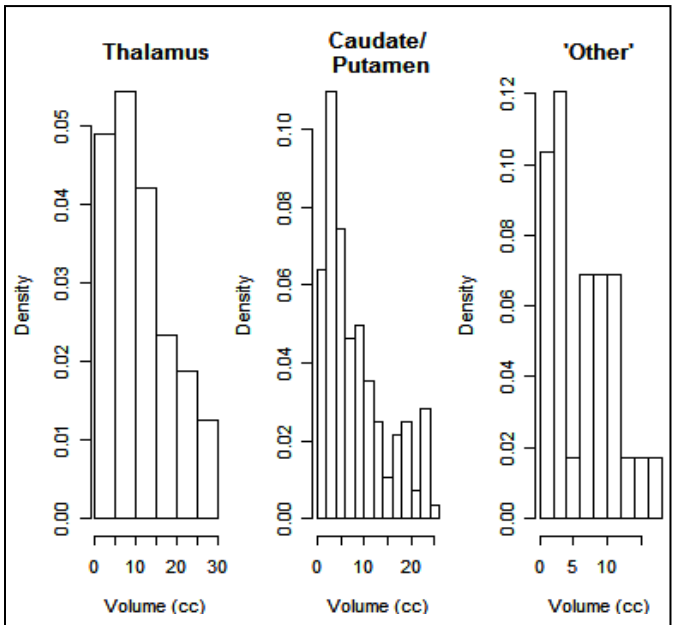


Fig. 2g-1. Joint distribution of clot locations and ICH volumes

Step 2: Simulate ICH volumes based on clot location. ICH volumes within the "No Measurable Clot" location were all 0cc. For the remaining clot locations, lognormal distributions of ICH volumes truncated at 30cc were used to account for design restrictions and skewness in the observed Safety, CLEAR A and CLEAR B ICH volumes. Calculated lognormal parameters (mean, standard deviation) were: Thalamus, (2.56, 0.73); Caudate\Putamen, (2.16, 0.86), other location, (1.42, 1.06). For our (N=500) simulation dataset 1, the resulting joint distribution of clot locations and ICH volumes is depicted in Figure 2g-1.

Step 3: Simulate IVH volumes based on ICH and clot location. In the Thalamus location, a linear regression of IVH volume on ICH volume with estimated relationship E(IVH) = 23.81 + 0.45(ICH), and residual standard deviation of 20.35 fit the data well. For the Caudate\Putamen location, a linear regression of IVH volume on ICH volume with estimated relationship E(IVH) = 57.51 + 0.15(ICH) and residual standard deviation of 39.48 was used. For the Other location, the IVH-ICH relationship was inverse, with parameter estimates of E(IVH) = 49.84 – 0.83(ICH) and residual standard deviation of 22.34. In the "No Measurable Clot" location, there was no information to estimate an IVH-ICH relationship, and thus IVH volume was simulated under a Gaussian model using the observed sample mean and standard deviation values of (mn=68.76, sd=37.79). Joint plots of the IVH volume, ICH volume, and clot location relationships are shown in Figure 2g-2.

Step 4: Simulate the rt-PA assignment based on IVH & ICH volumes, and clot location. The study design incorporated simple random allocation for treatment assignment. Hence, simulated EVD + rt-PA was a random coin flip with a 50% chance of receiving rt-PA.

Step 5: Simulate the mRankin outcomes based on the rt-PA assignment, IVH & ICH volumes and clot location. Parameter estimates for the categorical mRS outcomes observed in the Safety, CLEAR part A and part B studies were as follows: treatment effect: θ = 0.6 to 0.8 (i.e. odds-ratio of 1.8 to 2.2); IVH volume: b1 = -0.043; ICH volume b2 = -0.097; Clot Location: Thalamus: b3 = -0.83; Caudate\Putamen: b4 = 1.01; No Measurable Clot: b5 = -0.82. For a control rate (p0) approximately = 0.20, intercepts a_0 = -0.1, a_1 = 0.05, a_2 = 0.25, a_3 = 0.65, a_4 = 2.90, a_5 = 5.95 were used; for a control rate approximately = 0.30, intercepts a_0 = -0.5, a_1 = 0.2, a_2 = 0.75, a_3 = 1.5, a_4 = 3.04, a_5 = 5.55 were used. Additionally, site clustering or between-site heterogeneity was parameterized as a latent effect with standard deviation τ=.1 and .25, assuming approximately 50 sites. These values led to probability curves as depicted in Figure 2g-3, which shows the likelihood of attaining each mRS outcome across IVH volumes for the Thalamus clot location. The numbers directly above the probability curves denote the respective mRS score. Note that our observed data from the Safety and CLEAR part A study yields all seven probability curves shifted to the right under the EVD + rt-PA intervention, yielding higher success probabilities for lower (better) mRS outcomes. Given a subject's simulated clot location, ICH volume, IVH volume and treatment assignment, mRS outcome scores could then be drawn from a multinomial distribution with probabilities following these empirically observed relationships.

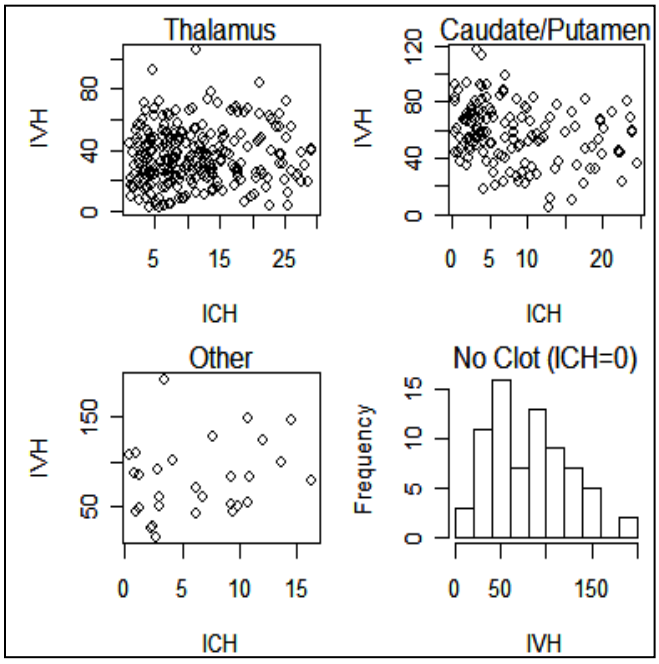


Fig. 2g-2. Joint plots of IVH, ICH volumes and clot location relationships

If we use this technique to draw a sample of mRS outcomes of size N=500 (proposed trial size), we inherently simulate one possible outcome of the proposed trial.
Following the five steps in this simulation procedure a large number of times, such as 1000, analyzing the resulting datasets each time and recording whether we obtain statistically significant treatment effect results at the 5% level leads to Monte Carlo estimates of the proposed trial's power to detect a treatment difference. Using this machinery, a variety of simulation scenarios were examined to judge the sensitivity of power towards sample size (N=500, 600 & 700), effect size (odds-ratio = 1.8 to 2.2), control group outcome rates (placebo rates of good outcome mRS $\leq$3 = 20%, 30%), model choice (correctly specified vs. non-correctly specified model), and site clustering (between site heterogeneity parameterized as a latent effect with standard deviation τ =.10 and .25 [i.e. 14% and 36% of log-odds-ratio treatment effect theta =.7 , (OR = 2.0), respectively]). Figure 2g-4 shows the power across varying levels of sample size and treatment efficacy parameter theta=log(OR) with a between site heterogeneity parameter τ=.10, for both dichotomized outcomes mRS $\leq$3 and mRS $\leq$4. P_0 represents the proportion of patients in the EVD + placebo group with good outcomes (mRS $\leq$ 3 or mRS $\leq$ 4).

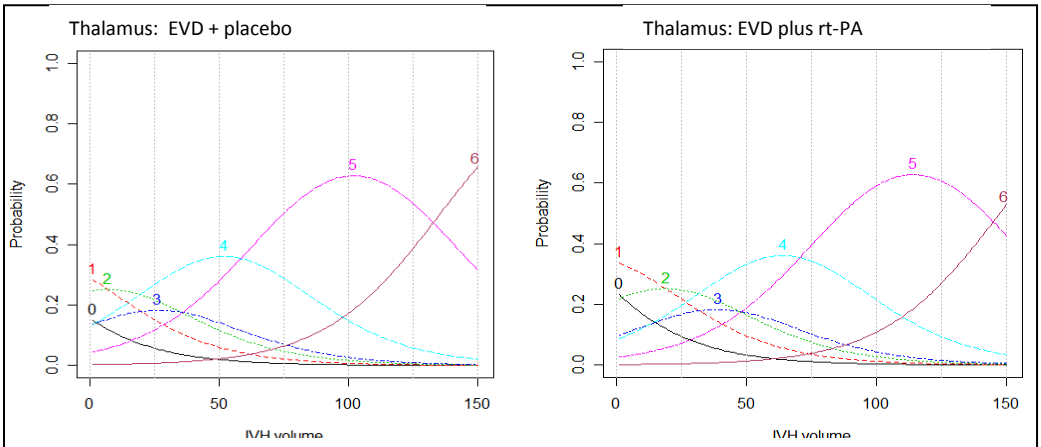


Figure 2g-3. Modified Rankin Score probabilities observed in the Safety and CLEAR Part A results used for Monte Carlo power study simulations.

Hence, the proposed sample size of N=500 adequately powered the trial to detect treatment effects around our previously observed treatment effect; clot removal with EVD + rt-PA resulting in a doubling of the odds of having a better mRS outcome when controlling for IVH and ICH volume and clot location. This corresponded with being able to determine an absolute difference of 15% or more in the probability of better outcomes comparing EVD + rt-PA and EVD + placebo groups, as specified in our primary hypothesis. Given our experience in controlling rebleeding and maximizing clot removal in the more recent CLEAR A and B studies, we expected the previously observed measure of $\theta = 0.7$ (OR = 2.0) to be a conservative estimate of the treatment effect.

Additional simulations were performed to examine sensitivity towards effects of a potential latent patient-severity factor based on an IVH volume > 60 cc. Inclusion of this factor in the simulation methodology did not change the overall power results.

Table 2g-1. Power Available to Detect Specified Effect With Alpha = 0.05 For Two Groups of Size 250 (Total of 500 patients)

	Proportion with Good Outcome in the EVD + placebo Management Group			
Effect size (Abs diff.)	20%	25%	30%	35%
25%	>.99	>.99	>.99	>.99
20%	>.99	>.99	>.99	>.99
15%	.96	.94	.92	.91
14%	.93	.91	.88	.87
13%	.89	.86	.84	.82
12%	.84	.80	.77	.75
11%	.78	.73	.70	.68
10%	.70	.65	.61	.59

Table 2g-2. Confidence intervals for event rates

Event Rate *	95% Confidence Interval Around Event Rate for		
	50 patients	125 patients	250 patients
.05	.013 -.165	.018 -.102	.025 -.082
.10	.033 -.218	.056 -.171	.066 -.144
.15	.072 -.291	.094 -.227	.106 -.198
.20	.100 -.337	.134 -.281	.152 -.255
.25	.146 -.403	.175 -.333	.196 -.306
.30	.179 -.446	.225 -.393	.244 -.361
.35	.229 -.508	.269 -.442	.289 -.411
.40	.264 -.548	.313 -.491	.339 -.464
.45	.318 -.607	.359 -.540	.385 -.512
.50	.355 -.645	.413 -.595	.436 -.564

* Or closest rate to this achievable with an integer number of events

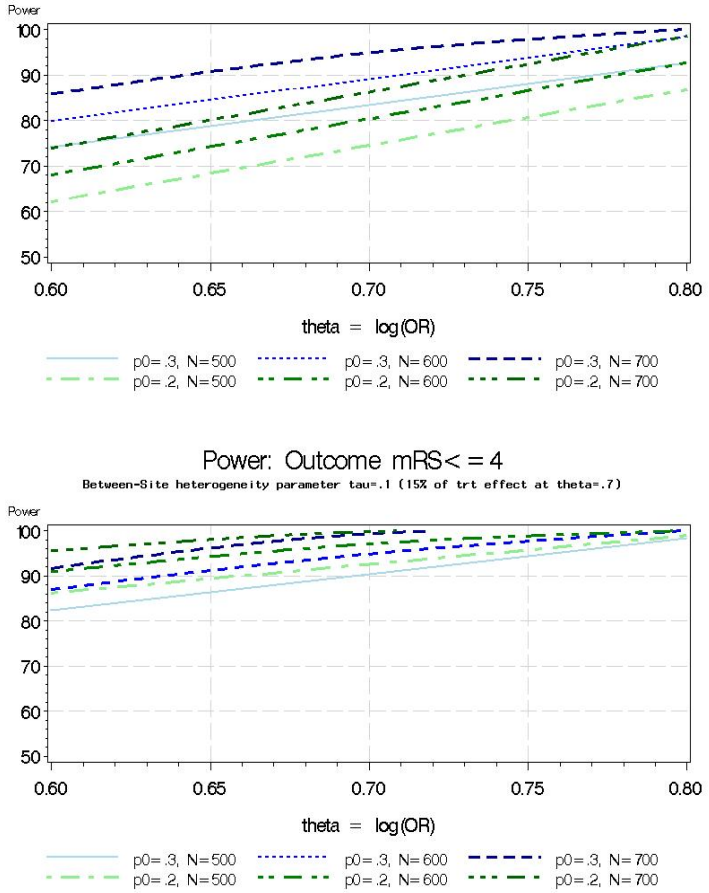


Figure 2g-4: Power curves from dichotomous mRS endpoints across varying levels of sample size and treatment effect [theta=log(OR)] for between site heterogeneity parameter τ=.10 (14% the effect size of the treatment efficacy at theta=.7). For N=500, power is greater than 80% for combinations of parameters near those observed in current studies (p0=.25, theta=.7).

In addition to the Monte Carlo simulations above, we investigated power for the primary endpoint 1 for a study designed to enroll a total of 500 patients through standard rate comparison power formulae. The power available to detect various effect sizes is shown for ranges between 20% to 35% of the current EVD + placebo group achieving a good outcome (such as mRS score ≤ 3) calculated using the normal approximation with continuity correction for a two sample test of equality of proportions (Table 2g-1).

2g.1.2. Statistical Power - Primary Endpoint 2 (Modified Rankin Scale as Ordinal Score at 180 days). Clot removal with EVD and treatment with low-dose rt-PA for IVH clot removal produces improved outcome(s) assessed by the ordinal mRS when compared to EVD + placebo (Fleiss, Statistical methods for rates and proportions, New York: John Wiley & Sons, Inc.; 1981). The power to detect difference between treatment groups may be enhanced by retaining the ordinal nature of the mRS, hence we expected greater than 85% power as in the simulations detailed above. Binomial exact 95% confidence intervals for groups of 50, 125 and 250 patients for

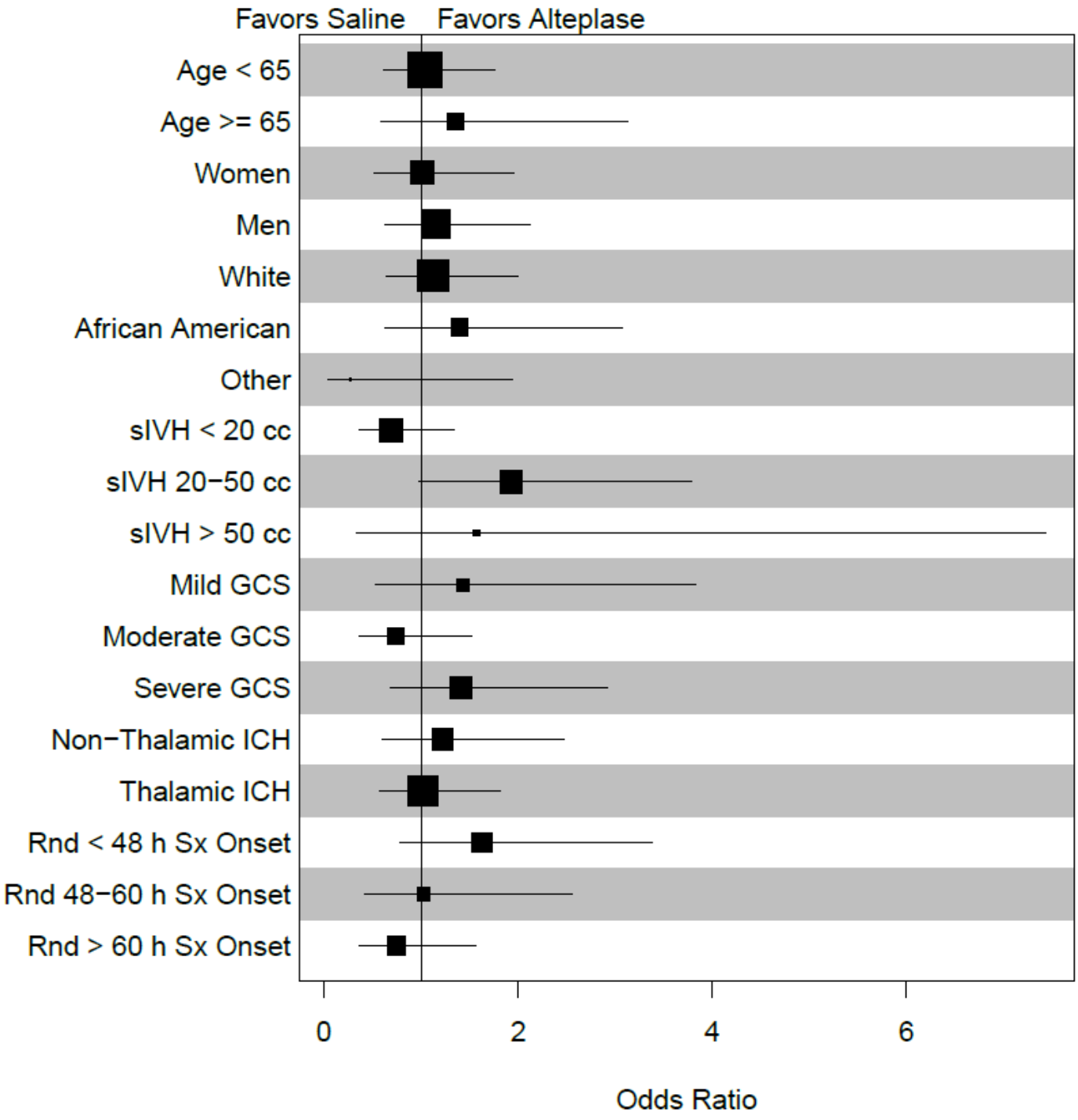
event rates ranging from 0.05 to 0.50 are shown in Table 2g-2. In terms of detecting differences in adverse event rates between the two groups, the study had 80% power, or better, to detect an increase of 0.125 in the rate of any event among the rt-PA treated patients provided the rate of that event experienced by patients who received EVD + placebo is at least 0.10. For example, if the bleeding or infection rate was 0.15 (15%) in the EVD + placebo group, the study had 80% power or better to detect a difference between the groups if the rate in the rt-PA group was 0.275 (27.5%) or higher.

2g.1.3. Statistical Power - Primary Endpoint 3 (Modified Rankin Scale ≤4 at 180 days). EVD and treatment with low-dose rt-PA for IVH clot removal produces improved outcome(s) using an alternate mRS cutoff at 180 days of mRS $\leq$ 4. Power for primary endpoint 3 was examined similarly to that for the primary endpoint 1. As in Figure 2g-4, there was greater than 80% power to detect mRS $\leq$ 4 in all situations examined in the Monte Carlo simulations.

3. Figures

3a. Figure S1. Subgroup analysis.

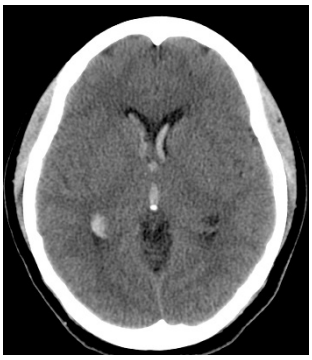
Forest plot of interaction terms, adjusted for age, gender, thalamic ICH location, stability ICH, IVH volume, and GCS (mild=13-15; moderate=9-12; severe=3-8) at admission. The size of points indicates the relative sizes of the subgroups. Scores on the Glasgow Coma Scale (GCS) range from 15 (fully conscious) to 3 (deep coma).

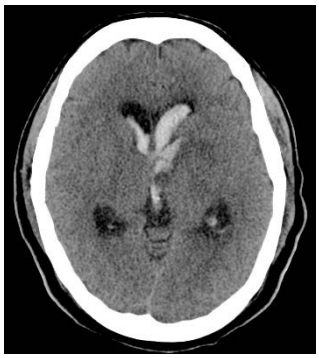


3b. Figure S2. CT images correlating to different IVH volumes.

Volumetric software (Osirix) was used to measure clot volume by outlining and totaling each region of interest (IVH, ICH, catheter tract, and other areas of bleeding. The images presented here are representative of the sub groups of IVH volume used for adaptive randomization (<20 mL, 20-50 mL, >50 mL).

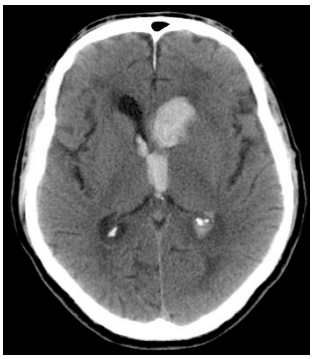
ICH: 0 cc
IVH: 8.3 cc

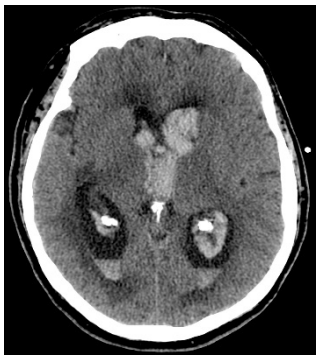




ICH: 7.17 cc
IVH: 18.3 cc

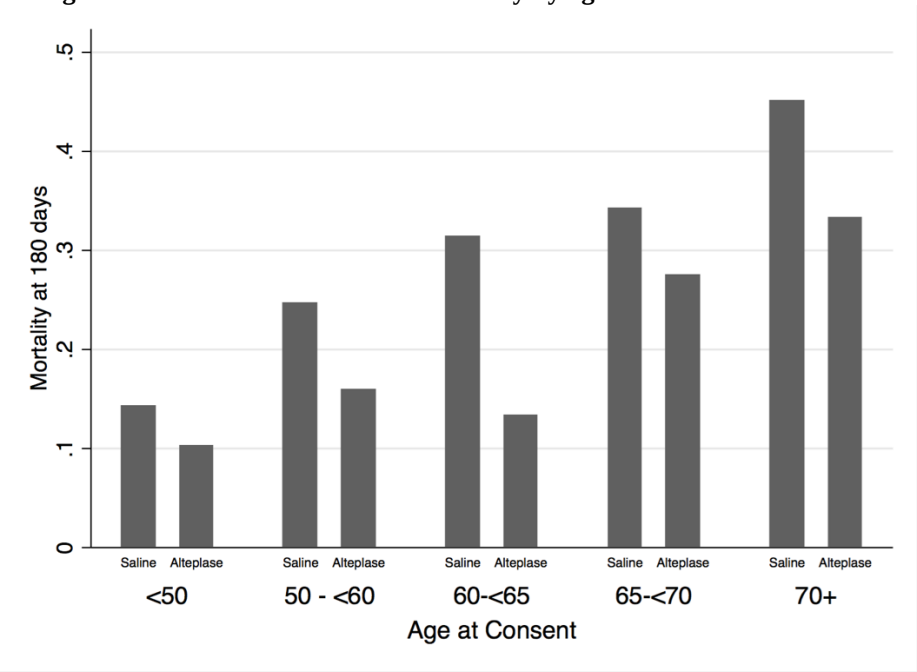
ICH: 6.3 cc
IVH: 32.6 cc



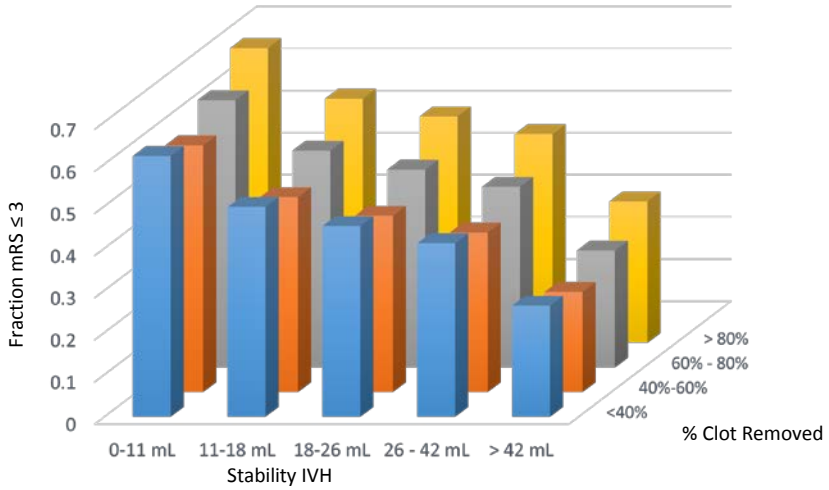


ICH: 1.31 cc
IVH: 52.2 cc

3c. Figure S3. Effect of treatment on mortality by age



3d. Figure S4. Relationship between mRS 0-3 and percent clot removed by IVH volume as determined at stability prior to randomization.



4. Tables

4a. Table S1. Primary and secondary analyses descriptive listing and corresponding results.

	Analyses	Results	Notes	Interpretation
Primary Outcomes				
1.1. 180 day mRS* (0-3)				
Univariate Treatment	Chi-Square Test	Alt: 47.6%, Sal: 44.9%. Risk Diff (95% CI) = 2.7% (-6.2%, 11.5%), p = 0.554		
Adjusted for IVH/ Thalamus	Wt-effect Across 6 Strata	Risk Diff (95% CI) = 3.5% (-4.2%, 11.9%)		
Full Adjustment	Multivariable Logit Model	Adj OR (95% CI) = 1.17 (0.74, 1.84), p = 0.496. OR for mRS <= 3 v. > 3; Alt v. Sal.	Adj for Age, GCS, Thal, Stab ICH, Stab IVH (cat)	No difference by random grp for mRS 0-3 proportion
1.2. mRS* as Ordinal Score	Unadj Prop Odds Model	OR (95% CI) = 0.81 (0.60, 1.11), p = 0.198. OR for mRS > K v. <= K; Alt v. Sal.	Null hypothesis of prop odds rejected; chi2 p = 0.025*	
	Adjust Prop Odds Model	Adj OR (95% CI) = 0.74 (0.53, 1.02), p = 0.068. Adj OR for mRS > K v. <= K; Alt v. Sal.	Adj for Age, GCS, Thal, Stab ICH, Stab IVH (cat)*	
			Null hypothesis of prop odds rejected; chi2 p = 0.018	
	Unadj Gen Ordered Logit Model for Ordered Data	OR (95% CI) = 0.90 (0.66, 1.24), p = 0.538. OR for mRS > K v. <= K if K = 1 - 4; Alt v. Sal.	Prop Odds satisfied for mRS 0, 1 - 4 assumed identical (chi 2 p=0.9967).*	
		OR (95% CI) = 0.55 (0.37, 0.81), p = 0.003. OR for mRS > 5 v. <= 5; Alt v. Sal.	Prop Odds satisfied for mRS 0, 1 - 4 assumed identical (chi 2 p=0.9967).*	Mortality less with random assignment to alteplase
	Adjust Gen Ordered Logit Model #1 for Ordered Data	Adj OR (95% CI) = 0.86 (0.62, 1.19), p = 0.379. Adj OR for mRS > K v. <= K if K = 1 - 4; Alt v. Sal.	Adj for Thal and Stab IVH (cat)*	
		Adj OR (95% CI) = 0.49 (0.32, 0.74), p = 0.001. Adj OR for mRS > 5 v. <= 5; Alt v. Sal.	Adj for Thal and Stab IVH (cat)*	Mortality less with random assignment to alteplase
	Adjust Gen Ordered Logit Model #2 for Ordered Data	Adj OR (95% CI) = 0.89 (0.63, 1.25), p = 0.497. Adj OR for mRS > K v. <= K if K = 1 - 4; Alt v. Sal.	Adj for Age, GCS, Thal, Stab ICH, Stab IVH (cat)*	
		Adj OR (95% CI) = 0.44 (0.28, 0.71), p = 0.001. Adj OR for mRS > 5 v. <= 5; Alt v. Sal.	Adj for Age, GCS, Thal, Stab ICH, Stab IVH (cat)*	Mortality less with random assignment to alteplase
1.3. 180 day mRS* (0-4)				
Univariate Treatment	Chi-Square Test	Alt: 64.2%, Sal: 61.6%. Risk Diff (95% CI) = 2.6% (-5.9%, 11.1%), p = 0.552		
Full Adjustment	Multivariable Logit Model	Adj OR (95% CI) = 1.22 (0.79, 1.88), p = 0.372. OR for mRS <= 3 v. > 3; Alt v. Sal.	Adj for Age, GCS, Thal, Stab ICH, Stab IVH (cat)	
1.4. Random Effects (mRS* 0-3)	Random Effects Model w/ site as random effect	OR (95% CI) = 1.11 (0.81, 1.53), p = 0.514. OR for good outcome Alt v. Sal. ICC = 1.3 X 10^-6	Unadjusted	No differences of mRS 0-3 attributable to site differences
	Adj Random Effects Model w/ site as random effect	Adj OR (95% CI) = 1.17 (0.77, 1.78), p = 0.461. OR for good outcome Alt v. Sal. ICC = 2.2 X 10^-7	Adj for Age, GCS, Thal, Stab ICH, Stab IVH (cat)	

	Analyses	**Results**	**Notes**	**Interpretation**
1.5. Longitudinal (mRS* 0-3)	Uadj GEE model (Logit mRS (0-3) at 30 and 180 days	30 Days: OR (95% CI) = 1.34 (0.85, 2.12) p = 0.207; 180 Days: OR (95% CI) = 1.10 (0.77, 1.57) p = 0.597		No between grp differences mRS 0-3 over time
	Adj GEE model (Logit mRS (0-3) at 30 and 180 days	30 Days: OR (95% CI) = 1.26 (0.75, 2.10) p = 0.384; 180 Days: OR (95% CI) = 1.01 (0.62, 1.64) p = 0.964	Adj for Age, GCS, Thal, Stab ICH, Stab IVH (cat)	
Secondary Outcomes				
2.1 All-Cause Mortality - 180 days	Log Rank Test	Mortality - Alt: 18.5%, Sal: 29.1%. P = 0.0056		Less mortality with random assignment to alteplase
2.2. Clot Removal	AUC / Logit Model	Adj OR (95% CI) = 0.96 (0.94, 0.97), p < 0.001. OR for mRS (0-3) per time-wt mL.	Adj for Trt, Age, GCS, Thal, Stab ICH	Greater clot removal associated with greater likelihood for mRS 0-3
IVH by Trt Interaction	Multivariable Logit Model	IVH < 20 mL - Adj OR (95% CI) = 0.69 (0.35, 1.38), p = 0.295. OR for mRS <= 3 Alt v. Sal.	Adj for Age, GCS, Thal, Stab ICH, Stab IVH (cat)	
		IVH >= 20 mL - Adj OR (95% CI) = 1.87 (1.02, 3.43), p = 0.044. OR for mRS <= 3 Alt v. Sal.		Per protocol analysis: greater mRS 0-3 in key randomized subgroup with assignment to alteplase
80% of Clot Removed	Multivariable Logit Model	Adj OR (95% CI) = 1.38 (0.82, 2.33), p = 0.226. OR for mSR (0-3) for >80% v. <= 80% Clot Removed	Adj for Age, GCS, Thal, Stab ICH, Stab IVH (cat)	
85% of Clot Removed	Multivariable Logit Model	Adj OR (95% CI) = 1.91 (1.03, 3.55), p = 0.040. OR for mSR (0-3) for >85 % v. <= 85% Clot Removed	Adj for Age, GCS, Thal, Stab ICH, Stab IVH (cat)	Threshold analysis- Post hoc- justified given finding of relationship to removal
90% of Clot Removed	Multivariable Logit Model	Adj OR (95% CI) = 2.25 (1.10, 4.58), p = 0.026. OR for mSR (0-3) for >90% v. <= 90% Clot Removed	Adj for Age, GCS, Thal, Stab ICH, Stab IVH (cat)	Threshold analysis- Post hoc- Justified given finding of relationship to removal
2.3. Critical Care Management	Rank Sum for skewed data (instead of linear regression), Chi-Square Test (in place of univariate logistic model)			
Hosp Days		Median (IQR) - Alt: 23 (17,31) days, Sal: 24 (16,31), p = 0.771		
ICU Days		Median (IQR) - Alt: 14 (11,21) days, Sal: 15 (12, 22), p = 0.098	Alt: 15 (12,22), Sal: 16 (13, 23), p=0.23	
Critical Care Complications				
ICP Management	Generalized Linear Models	Mean proportion of events of ICP >20mmHg – Alt: 9.8 mmHg, Sal: 10.2 mmHg, p = 0.450	Mean of patient-specific proportions	
Mechanical ventilation		Alt: 73.9%, Sal: 76.5%, p=0.501		

	Analyses	Results	Notes	Interpretation
Pressors		Alt: 60%:Sal: 63%, p=0.795		
Use of Shunts		Alt: 18.5%, Sal: 17.5%, p=0.784		
All infections Day 30 (SR)		Alt: 48.2%, Sal: 50.6%, p=0.592		
pneumonia day 30		Alt: 26.1%, Sal: 32.7%, p=0.105		
All infections Day 180 (SR)		Alt: 49.8%, Sal: 56.2%, p=0.152		
2.4. 30-Day Mortality / Safety	Fisher's Exact Test (was used instead of univariate logistic model due to small cell size)			
Mortality w/in 30 days		Alt: 8.8%, Sal: 14.3%. Risk Diff (95% CI) = -5.5% (-11.1%, 0.08%), p = 0.055	Bar Plot in ISC Slides (Hanley Talk). Email 2/9/16	
Bacterial Brain Infections		Alt: 6.8%, Sal: 10.4%. Risk Diff (95% CI) = -3.5% (-8.4%, 1.4%), p = 0.202		
Systematic Bleeds w/ 72 hours		Alt: 2.4%, Sal: 2.0%. Risk Diff (95% CI) = 0.42% (-2.2%, 3.0%), p =0.771		
Systematic Bleeds w/ 30 days		Alt: 3.6%, Sal: 3.2%. Risk Diff (95% CI) = 0.43% (-2.8%, 3.6%), p =0.811		
2.5. AE / SAE	Fisher's Exact Test (was used instead of univariate logistic model due to small cell size)	Alt: 48.6%, Sal: 62.9%. Risk Diff (95% CI) = -14.4% (-23.0%, -5.74%), p = 0.002		Fewer subject with SAEs in the alteplase grp
Brain infections day 180 (SR)		Alt: 7%, Sal: 12%, p=0.047		Fewer brain infections at 180 days in the alteplase grp
2.6. Predictors of Mortality	Unadjusted Cox Proportional Hazards Model	HR (95% CI) = 0.59 (0.41, 0.86), p = 0.006; Alt v. Sal		Model shows random assignment to alteplase associated with lower mortality
	Unadjusted Cox Proportional Hazards Model	Adj HR (95% CI) = 0.58 (0.40, 0.85), p = 0.005; Alt v. Sal	Adj for Age, GCS, Thal, Stab ICH, Stab IVH (cat)	Adjusted model shows random assignment to alteplase associated with lower mortality
2.7. Sub-Group Analyses	Chi-Square Test - Difference in mRS 0-3 proportion			
Race (AA)		AA - Alt: 54.4%, Sal: 48.0%. Risk Diff (95% CI) = 6.4% (-8.8%, 21.7%), p = 0.410	N = 165	
Race (White)		White - Alt: 43.4%, Sal: 41.8%. Risk Diff (95% CI) = 1.6% (-9.6%, 12.8%), p = 0.781	N = 301	
Gender(Female)		Female - Alt: 47.6%, Sal: 45.6%. Risk Diff (95% CI) = 2.0% (-11.3%, 15.2%), p = 0.773	N = 217	

	Analyses	Results	Notes	Interpretation
Gender (Male)		Male - Alt: 47.6%, Sal: 44.3%. Risk Diff (95% CI) = 3.2% (-8.5%, 15.1%), p = 0.587	N = 274	
Age (<= 65 yr)		<= 65 - Alt: 53.6%, Sal: 52.1%. Risk Diff (95% CI) = 1.5% (-9.0%, 12.1%), p = 0.775	N = 346	
Age (> 65 yr)		> 65 - Alt: 31.3%, Sal: 29.5%. Risk Diff (95% CI) = 1.9% (-13.2%, 16.9%), p = 0.808	N = 145	
IVH (≤20 mL)		< 20 - Alt: 55.1%, Sal: 58.3%. Risk Diff (95% CI) = -3.3% (-16.5%, 9.9%), p = 0.625	N = 217	
IVH (20 - 50mL)		20 - 50 - Alt: 47.3%, Sal: 38.5%. Risk Diff (95% CI) = 8.7% (-4.3%, 21.8%), p = 0.191	N = 219	
IVH (> 50 mL)		> 50 - Alt: 18.5%, Sal: 17.9%. Risk Diff (95% CI) = 0.66% (-19.7%, 21.1%), p = 0.949	N = 55	
Location (Thalamic)		Thalamic - Alt: 38.8%, Sal: 37.4%. Risk Diff (95% CI) = 1.4% (-9.8%, 12.6%), p = 0.812	N = 286	
Location (Non-Thalamic)		Non-Thalamic - Alt: 60.6%, Sal: 54.7%. Risk Diff (95% CI) = 5.9% (-7.6%, 19.4%), p = 0.394	N = 205	
Severity Index	Regression of Treatment by subject severity level	Adj OR (95% CI) = 0.37 (0.31, 0.44), p < 0.001. Odds for mRS 0-3 decreases for each unit increase in severity score	Severity score includes age, GCS, Thalamic location, Stab IVH, Stab ICH.	Assignment to alteplase did not improve mRS but did improve mortality (See Suppl section 2d.)
2.8. Functional Status				
NIHSS[†]	Rank Sum	Mean (SD) - Alt: 5.0 (7.0), Sal: 6.1 (7.9), p = 0.140	N (Alt) = 182, N (Sal) = 158	
Barthel[‡]	Rank Sum	Mean (SD) - Alt: 65.2 (37.7), Sal: 69.5 (35.1), p = 0.312	N (Alt) = 197, N (Sal) = 170	
eGOS[§] (>= Up SD v. <= Low SD)	Chi-Square Test	Alt: 39.4%, Sal: 32.0%. Risk Diff (95% CI) = 7.5% (-1.1%, 16.0%), p = 0.087		
eGOS[§] (>= Up SD v. <= Low SD)	Multivariable Logit Model	Adj OR (95% CI) = 1.53 (0.97, 2.41), p = 0.069. OR for >= Up SD; Alt v. Sal.	Adj for Age, GCS, Thal, Stab ICH, Stab IVH (cat)	
eGOS[§] ordinal	Generalized Ordinal Model Test of Proportionality unadjusted eGOS (chi 2 p = 0.306 for Prop Odds)	OR (95% CI) = 0.67 (0.48, 0.93), p = 0.016. OR for eGOS > K v. <= K; Alt v. Sal.	Reverse coded: 5 - death, 4 - VS+low SD, 3 - up SD, 2 - MD, 1 – GR	Proportional shift favors alteplase when all levels of eGOS considered.
eGOS[§] ordinal	Adjust Gen Ordered Logit Model for Ordered Data	Adj OR (95% CI) = 1.40 (0.67, 2.92), p = 0.370. Adj OR for eGOS MD or worse v. GR; Alt v. Sal.	Reverse coded: 5 - death, 4 - VS+low SD, 3 - up SD, 2 - MD, 1 – GR	
		Adj OR (95% CI) = 0.93 (0.56, 1.54), p = 0.786. Adj OR for eGOS Up SD or worse v. MD + GR.; Alt v. Sal.	Partial Proportional Odds Model: GR (low + up) and MD (low + up) identical	
	Test of proportionality, (VS+low SD), and MD, GR assumed identical (chi 2 p=0.080).	Adj OR (95% CI) = 0.61 (0.39, 0.94), p = 0.025. Adj OR for eGOS (VS+low SD) + Death v. Up SD + MD+ GR; Alt v. Sal.		eGOS identifies groups different for VS, low SD, and mortality
		Adj OR (95% CI) = 0.48 (0.30, 0.77), p = 0.002. Adj OR for eGOS Death v. (VS+ low SD) + Up SD + MD + GR.; Alt v. Sal.		eGOS identifies groups different for mortality
2.9. QoL	T-test			QoL not different by Grp
SIS[‖] (Strength)		Mean - Alt: 55.0, Sal: 58.8, p = 0.312		
SIS[‖] (Mobility)		Mean - Alt: 58.3, Sal: 60.1, p = 0.652		

	Analyses	**Results**	**Notes**	**Interpretation**
SIS[l] (Hand Function)		Mean - Alt: 53.4, Sal: 56.5, p = 0.478		
SIS[l] (ADL)		Mean - Alt: 59.3, Sal: 61.2, p = 0.634		
SIS[l] (Communication)		Mean - Alt: 76.0, Sal: 79.6, p = 0.255		
SIS[l] (Thinking)		Mean - Alt: 58.5, Sal: 62.7, p = 0.224		
SIS[l] (Emotion)		Mean - Alt: 73.1, Sal: 73.5, p = 0.882		
SIS[l] (Participation)		Mean - Alt: 47.5, Sal: 49.6, p = 0.551		
EuroQol Vas[¶]		Mean (SD) - Alt: 62.8 (26.0), Sal: 65.1 (23.3), p = 0.376		
	Accept Null			
	p<0.05 – Reject Null			

[*]Scores on the modified Rankin Scale (mRS) range from 0 (no disability) to 5 (severe disability) to 6 (death); for ordinal analysis, mRS 0 and 1 combined
[†]Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 (no disability) to 42 (severe disability)
[‡]Scores on the Barthel Index (BI) range from 0 (unable to perform any) to 100 (able to perform all) activities of daily living
[§]Scores on the Extended Glasgow Outcome Scale (eGOS) range upper good recovery to death
[l]Scores on the Stroke Impact Scale (SIS) range from 1 (most impaired) to 5 (no impairment) on 16 activity domains
[¶]Scores on the EuroQuol Visual Analog Scale (EQ-VAS) range from 0 (worst) to 100 (best) imaginable health state

4b. Table S2. eGOS score frequencies for the 30, 180, and 365 day time points.

	Visit and Treatment							
	30 days				180 days			
eGOS	Saline		Alteplase		Saline		Alteplase	
Upper GR	4	1.62	3	1.23	17	7.05	15	6.22
Lower GR	4	1.62	1	0.41	5	2.07	6	2.49
Upper MD	2	0.81	10	4.12	12	4.98	13	5.39
Lower MD	4	1.62	9	3.70	10	4.15	19	7.88
Upper SD	19	7.69	19	7.82	33	13.69	42	17.43
Lower SD	132	53.44	138	56.79	85	35.27	92	38.17
VS	46	18.62	41	16.87	6	2.49	8	3.32
Dead	36	14.57	22	9.05	73	30.29	46	19.09
Totals	277	100.0	243	100.0	241	100.0	241	100.0

4c. Table S3. Univariable and Multivariable Analyses of Dichotomized mRS Modified Rankin Scale (mRS) Score at Day 180 (mRS 0-3 vs. 4-6); Illustrating the Influences of Treatment (alteplase vs. saline), Several Disease Factors, and Effect of Clot Removal on mRS score at Day 180 Outcome.

	Univariable (Unadjusted) Models	Multivariable Model 1 (All Patients)	Multivariable Model 2 (Treatment by IVH interaction at 20 mL)[1]
Variables	OR[2] [95% CI]	AOR[3] [95% CI]	AOR [95% CI]
Age (per year increase)	0.94* [0.93, 0.96]	0.95* [0.93, 0.97]	0.94* [0.92, 0.96]
Randomization GCS[†] (per unit increase)	1.27* [1.20, 1.36]	1.21* [1.13, 1.30]	1.21* [1.12, 1.30]
ICH Location (Thalamic v. Other)	0.45* [0.31, 0.65]	0.46*** [0.26, 0.83]	0.44** [0.24, 0.81]
Stability ICH (per mL)	0.90* [0.87, 0.92]	0.90* [0.87, 0.94]	0.89* [0.86, 0.93]
AUC normalized (per mL of time-weighted clot volume remaining)	0.96* [0.95, 0.98]	0.96* [0.94, 0.97]	
Treatment – All Patients (rt-PA v. saline)	1.11 [0.78, 1.59]	0.92 [0.59, 1.44]	
Treatment – IVH > 20 mL (alteplase vs. saline)	1.36 [0.84, 2.23]		1.87*** [1.02, 3.43]

[1] Model also adjusts for stability IVH; [2] OR: odds ratio; [3] AOR: adjusted odds ratio
[†] Scores on the Glasgow Coma Scale (GCS) range from 15 (fully conscious) to 3 (deep coma)
*p < 0.001; **p < 0.01; ***p < 0.05

4d. Table S4. Additional outcome variables by group.

Outcome Variables	Alteplase (N=249)	Saline (N=251)	p-value
eGOS[§] ≥ Upper SD at 180 days: no. (%)	95 (39)	77 (32)	0.087
Time to Home[ǀ]: Median (25th percentile)	95 (42)	107 (50)	0.771
Location at D180: no. (%)	249 (100)	251 (100)	0.062
Home: no. (%)	1378 (55)	1243 (49)	
Rehab Unit: no. (%)	27 (11)	18 (7)	
Acute: no. (%)	4 (2)	5 (2)	
Long-Term Care Facility: no. (%)	343 (143)	29 (12)	
Dead: no. (%)	46 (18)	73 (29)	
Missing: no. (%)	1 (<1)	32 (1)	
EuroQoL Visual Analog Scale (EQ-VAS)[¶]: Median [IQR]	70 [50, 80]	70 [50, 80]	0.497
Barthel Index (BI)[1]: Median [IQR]	85 [30, 100]	85 [45, 100]	0.312

[§]Scores on the Extended Glasgow Outcome Scale (eGOS) range from upper good recovery to death
[ǀ]25th percentile provided in place of IQR. Data censored at 180 days for analysis and 75% of subjects were not yet home.
[¶]Scores on the EuroQuol Visual Analog Scale (EQ-VAS) range from 0 (worst) to 100 (best) imaginable health state
[1]Scores on the Barthel Index (BI) range from 0 (unable to perform any) to 100 (able to perform all) activities of daily living

4e. Table S5. Primary reason for exclusion by count and frequency.

Primary Exclusion Criteria	Subject Count (n=9,784)	Frequency (%)
Structural etiology (aneurysm, Moyamoya, etc.)	1,312	13.4
Outside allowed age range	1,280	13.1
Lack of 3rd/4th obstruction	1,266	12.9
ICH volume greater than 30cc	1,250	12.8
No EVD placed	1,239	12.7
Infratentorial involvement	739	7.6
DNR status	347	3.6
Historic Rankin	158	1.6
Uncontrolled PTT, PLT, INR	157	1.6
Other Exclusion	2,036	20.7

4f. Table S6. Demographics for screen failures vs. enrolled subjects.

Demographic	**Screen Failures** (n=9,784)	**Enrolled** (n=500)	**p-Value** (Chi-Square w/Yates)
Gender			
Female	4,604 (47.1%)	222 (44.4%)	0.156
Male	5,138 (52.5%)	278 (55.6%)	
Unspecified	42 (0.4%)	0 (0.0%)	
Primary Diagnosis			
ICH with IVH	7,604 (77.7%)	428 (85.6%)	
Primary IVH	1,286 (13.1%)	72 (14.4%)	<0.00001
Unspecified	894 (9.1%)	0 (0.0%)	
Race			
White	6,624 (67.7%)	306 (61.2%)	
African-American	1,762 (18.0%)	170 (34.0%)	<0.00001
Asian	358 (3.7%)	14 (2.8%)	
Other/Unspecified	1040 (10.6%)	10 (2.0%)	

4g. Table S7. Proximate causes of death.

Proximate causes of death for subjects who died prior to 30 days and 30 or more days post symptom onset but prior to completing the day 180 visit.

	< 30 Days			**30-180 Days**			**0-180 Days Combined**
Proximate Cause of Death	**Alteplase**	**Placebo**	**Total**	**Alteplase**	**Placebo**	**Total**	**Total**
Neurologic no. (%)	17 (73.91)	26 (74.29)	43 (74.14)	7 (30.43)	13 (34.21)	20 (32.79)	63 (52.94)
Cardiac no. (%)	3 (13.04)	3 (8.57)	6 (10.34)	3 (13.04)	6 (15.79)	9 (14.75)	15 (12.61)
Respiratory no. (%)	2 (8.70)	2 (5.71)	4 (6.90)	3 (13.04)	8 (21.05)	11 (18.03)	15 (12.61)
Renal no. (%)	0 (0.00)	0 (0.00)	0 (0.00)	1 (4.35)	1 (2.63)	2 (3.28)	2 (1.68)
Gastrointestinal no. (%)	1 (4.35)	0 (0.00)	1 (1.72)	1 (4.35)	0 (0.00)	1 (1.64)	2 (1.68)
Infection, non-neurologic no. (%)	0 (0.00)	3 (8.57)	3 (5.17)	4 (17.39)	2 (5.26)	6 (9.84)	9 (7.56)
Unknown no. (%)	0 (0.00)	1 (2.86)	1 (21.52)	4 (17.39)	8 (21.05)	12 (19.67)	13 (10.92)
Total no.	**23**	**35**	**58**	**23**	**38**	**61**	**119**

4h. Table S9. Premorbid, historical modified Rankin Scale scores by treatment group.

Historical mRS*	Alteplase	Saline	Total
0 no. (%)	219 (50.1)	218 (49.9)	437 (100)
1 no. (%)	30 (48.4)	32 (51.6)	62 (100)
2 no. (%)	0 (0.0)	1 (100.0)	1 (100)
Total no. (%)	249 (49.8)	251 (50.2)	500 (100)

*Scores on the modified Rankin Scale (mRS) range from 0 (no disability) to 5 (severe disability) to 6 (death)

4i. Table S10. Effect of treatment on mortality by age (data from Figure S4 in tabular format)

	5 Age Categories				
Treatment	**<50**	**50 - <60**	**60-<65**	**65-<70**	**70+**
Saline (n)	49	81	35	35	51
Mortality %	14.0%	25.0%	31.0%	34.0%	45.0%
Alteplase(n)	58	75	45	29	42
Mortality %	10.0%	16.0%	13.0%	28.0%	33.0%

4j. Table S11. Summary of Key Primary and Secondary Analyses and Results from Supplemental Table S1.

PRIMARY				
			Saline – Alteplase Difference (95% CI)	
1.1	Functional Outcome	3% increase mRS 0-3	3 (-6, 12)	p=0.587
1.2 – 1.5	Alt. Analyses of mRS Levels	mRS 6 half as likely with alteplase	0.5 (0.4, 0.8)	p<0.001
KEY SECONDARY				
2.1	180-day Mortality Outcome	11% decrease with alteplase	11 (3, 8)	p=0.007
2.2	Clot Removal	Associated with greater % mRS 0-3	---	p<0.001
2.3	ICU Care	No difference		p=0.098
2.4	30-day Mortality/Safety	Trend favors alteplase		p=0.055
2.5	Safety-AEs/SAEs	14% fewer SAEs with alteplase 5% less ventriculitis @ 180 days with alteplase	-14 (-23, -6) -5 (10.7, 0.4)	p=0.001 p= 0.047
2.6	Predictors of Mortality	Adjusted hazard of death 0.58	0.5 (0.4, 0.9)	p=0.005
2.7	Sub-group	No differences		NS (all listed in Table S1)

5. REFERENCES

1. Ziai WC, Tuhrim S, Lane K, et al. A multicenter, randomized, double-blinded, placebo-controlled phase III study of Clot Lysis Evaluation of Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III). International Journal of Stroke 2014;9:536-42.

2. Josephson CB, White PM, Krishan A, Al-Shahi Salman R. Computed tomography angiography or magnetic resonance angiography for detection of intracranial vascular malformations in patients with intracerebral haemorrhage. The Cochrane Library 2014.

3. Morgenstern L, Hemphill 3rd J, Anderson C, et al. American Heart Association Stroke Council and Council on Cardiovascular Nursing. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2010;41:2108-29.

4. Broderick J, Connolly S, Feldmann E, et al. American Stroke Association Stroke Council; American Heart Association/American Stroke Association High Blood Pressure Research Council; Quality of Care and Outcomes in Research Interdisciplinary Working Group. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American heart association/American stroke association stroke council, high blood pressure research council, and the quality of care and outcomes in research interdisciplinary working group. Circulation 2007;116:e391-413.

5. Mould WA, Carhuapoma JR, Muschelli J, et al. Minimally invasive surgery plus recombinant tissue-type plasminogen activator for intracerebral hemorrhage evacuation decreases perihematomal edema. Stroke 2013;44:627-34.

6. Morgan TC, Dawson J, Spengler D, et al. The modified Graeb score an enhanced tool for intraventricular hemorrhage measurement and prediction of functional outcome. Stroke 2013;44:635-41.